CANCER IN ONTARIO 1 [illegible]

SCREENING FOR CANCER

OCTF

The Ontario [illegible]

The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(b) the transportation of patients and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(d) the laboratory and clinical investigation of cancer problems;

(e) the co-ordination of facilities for treatment;

(f) the adequate reporting of cases and the recording and compilation of data;

(g) the education of the public in the importance of early recognition and treatment;

(h) the providing of facilities for undergraduate and postgraduate study;

(i) the training of technical personnel; and

(j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

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CANCER IN ONTARIO 1988

THE COVER

Early recognition of breast cancer can prevent deaths from the disease; screening of selected populations helps to detect these lesions in the early stages. Our cover illustrates the selection for examination of asymptomatic women between ages 50 to 65 - the square frame in colour, drawn from the general population - the remainder of the cover in black and white. Without organized programs, focussed on age groups known to be at greatest risk, scarce resources will be wasted and many lives lost that otherwise would be saved.

SCREENING FOR CANCER

The Ontario Cancer Treatment and Research Foundation
7 Overlea Boulevard,Toronto, Ontario, Canada, M4H 1A8

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MESSAGE FROM THE CHAIRMAN

Photo: Tony V. Hauser

As many of you are aware, the cost of our present system of health care is presenting difficult challenges to government and to society in general. With continuing exponential growth of new cases referred to our Centres in the order of 8% per year, we are again facing an operating deficit in 1988-89. At our urging, the Ministry of Health is carrying out an operational review to assess the reasons for the Foundation's continued financial difficulties.

Growth is also reflected in increased needs for Centres, equipment and lodges. On June 10, 1988, Premier David Peterson opened the fine new London Regional Cancer Centre; for this much credit must go to to Dr. H. Bush, former Director, and Dr. L. Levin, the present Director, the Victoria Hospital Corporation, and the Canadian Cancer Society Ontario Division. The new Northeastern Ontario Regional Cancer Centre in Sudbury is under construction and scheduled to open in 1990. The Toronto-Bayview Centre hopes to occupy the previously excavated basement and plans are being completed for a full expansion in the future. We are grateful to the City of North York, which will provide $1 million towards clinical equipment for the expanding Centre. In the meantime, the Foundation, in co-operation with the Sunnybrook Medical Centre and the University of Toronto, will contribute to the cost of a research tower adjacent to the expanded Centre. We hope the Premier will join us in August for the sod turning of the new Hamilton Centre. We continue to review plans for expansion or provision of additional space in Ottawa, Thunder Bay, and Windsor. It is with pleasure that I record the official opening on May 18, 1988, of the first linear accelerator in the Windsor Centre. On October 28, 1988, the expanded Maurice Grimes Lodge was opened at the Ottawa Regional Cancer Centre (Civic Division). We are grateful to the Canadian Cancer Society Ontario Division for making possible the completion of this special capital project.

Under the capable direction of Mr. John Mabley, the Ontario Cancer Care Fund is being reorganized to raise $50 million for the Foundation and the Ontario Cancer Institute.

1988 will be remembered as a watershed year because we have come to an agreement with Government to merge with the Ontario Cancer Institute to form "Ontario Cancer Control Agency". In 1989, details will become available and we anticipated that the Cancer Act will be revised shortly to begin the implementation of this historic undertaking.

With regret I record the death, on March 20, 1988, of the Hon. R.A. Bell, who served on the Board of the Foundation with distinction until 1987. For their services to the Board, I wish to thank Dr. N. Pohran, who resigned, and Mr. G. Ross, whose term expired. We welcome the renewal of the terms of Drs. B. Thall and L. Siminovitch. My opportunity to serve the Foundation as Chairman has been extended to April 1989.

In closing I wish to thank, through their Government, the people of Ontario, the Canadian Cancer Society Ontario Division, the staff of the Regional Cancer Centres and Head Office, the Ontario Cancer Institute, host hospitals and medical schools; their continued support has made our programs of patient care, research and education meaningful realities.

Michael A. Meighen, Q.C.
Chairman

EXECUTIVE DIRECTOR REPORTS

The Chairman has referred to the impact of our growth in patient referrals on our capital and operating costs. To growth pressure are added the costs of medical inflation -- drugs, equipment, etc., which exceeds general inflation, plus the natural desire to improve the scope of patient care, e.g. psychosocial support, research and education. These pressures have produced yet-another projected deficit for 1988-89 and has led us to difficult current and proposed measures to contain costs. I wish to thank my colleagues in all segments of the Foundation for their understanding of some of these constraints which we hope will be short-term. Also, we hope that the current operational review will provide guidelines for dealing more effectively with future challenges.

Growth in patient load and in the programs needed to care for them has made us a larger and more complex health care system, which requires periodic review of our organizational structure and management skills. An excellent manager workshop, organized by Miss Loraine MacLean of Human Resources, proved to be a well-received and successful beginning to improved management. Human Resources is implementing improved labor relations processes, plans to introduce a performance appraisal system to address pay equity, and to implement a plan for complying with the French Language Act.

In a busy year, Information Systems has completed a needs study for a renewed computer-based oncology patient management system in the Regional Cancer Centres, has continued its review of the needs of the Ontario Cancer Registry, and is making a systematic assessment of the needs of administration, finance and human resources. The details of these achievements are recorded elsewhere in this volume (Information Systems section).

The Research Advisory Panel, under the leadership of Drs. L. Siminovich and J. Laidlaw, has carried out an extensive review and refinement of our research program designed to address better the needs of the Regional Cancer Centres and the Division of Epidemiology and Statistics. This is reported in more detail elsewhere.

Dr. E.A. Clarke and her colleagues have spent many hours over the past year on our proposal for an organized breast screening program. We anticipate Government approval for this project in early 1989.

Our proposal, developed by Drs. W.M. Hryniuk, J. Gowing and their colleagues, for community cancer clinics networked to the Regional Cancer Centres is still under review by Government.

Congratulations are due to Dr. J. Kotalik and the staff of the Thunder Bay Regional Cancer Centre for their superb organization of the Foundation's 25th Clinical Conference on Early Cancer Detection and Management held on September 16, at Lakehead University.

On July 1, Dr. Gordon E. Catton retired as Director of the Ottawa Regional Cancer Centre and Dr. William K. Evans "took over the reins". To Gordon, thank you for your faithful service and, to Bill, welcome to the challenges of the Ottawa Centre past, present and future.

With regret I record the deaths on February 14 of Dr. Prabhat Banerjee -- a faithful radiation oncologist in the London Centre, and on March 6 of Dr. A.H. Sellers, an outstanding statistician and epidemiologist.

Space does not permit me to record all OCTRF staff changes but I welcome the new and thank those who have retired or moved on.

I wish to record my gratitude to Dr. R.S. Bush, who resigned as Director of the OCI/PMH during 1988, and to welcome Dr. D.R. Carlow as his successor. A working liaison with the OCI/PMH, which from the beginning has been an integral part of the Foundation's programs, will become even more important as we move into a merged Ontario Cancer Control Agency.

I wish to congratulate the Canadian Cancer Society which celebrated its 50th anniversary in 1988. In October, to celebrate this event, the Society, with the support of Health and Welfare Canada, organized a consensus conference entitled "Cancer Control in Canada: The Challenge to Co-ordinate". Participants from across the nation represented most, if not all, the constituencies relevant to oncology. As a result, a National Taks Force is being established to review and recommend on cancer control at the national, provincial and local levels.

In closing I wish to thank the Members of the Board, the Directors of the Regional Cancer Centres and their staff, and Head Office for their loyal support in these challenging, changing and fiscally difficult times. Finally, I wish to acknowledge the support of the Government of Ontario, the Canadian Cancer Society Ontario Division and the many patients, their families and friends without whose help we could not complete our task.

J.W. Meakin, M.D., C.M.
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the Head Office of the Foundation.

OBITUARIES

Dr. Prabhat Banerjee
1928-1988

Dr. Prabhat Banerjee, senior physician on the staff of the London Regional Cancer Centre (formerly the London Clinic) of the Ontario Cancer Treatment and Research Foundation died on February 14, 1988 in his 60th year. His death followed a prolonged illness and was a result of cancer -- the disease to which he had devoted his entire professional life.

Prabhat Banerjee was born in Calcutta, India, the son of Dr. Radakrishna and the late Sovarari Banerjee and received his early education and medical qualifications there. He chose radiotherapy as his speciality and in 1957 went to Manchester, England, to complete his training by earning his DMRT (England) and the FFR (now the FRCR). He served on the staff of the Christie Hospital and Holt Radium Institute until 1964 when he emigrated to London, Ontario. There he joined the staff of the London Clinic and the faculty of the University of Western Ontario as a member of the Department of Therapeutic Radiology. In both positions he assumed increasingly senior responsibilities until his death. For many years, he conducted outreach clinics in Wingham, Kitchener-Waterloo, and Cambridge, Ontario and to countless patients in those areas, who loved him dearly, he represented the "Cancer Clinic".

I first met Prabhat Banerjee in April 1957 when I went to Manchester to complete my training in radiotherapy. He quickly became a member of our family and, after my return to Canada in 1958, I persuaded him to emigrate and in 1964 he joined the London Clinic staff. As a colleague his intelligence, humor and devotion to his work made him invaluable; however, it was his compassion that made him a special person and endeared him to many who will never forget him.

He leaves a devoted wife, Lelia (Lea) nee Perkins, and two loving sons, Ross and Neal, who were devastated by his death.

J.C.M. Fetterly, M.D.
Radiation Oncologist
Victoria Cancer Clinic
Cancer Control Agency
of British Columbia

Dr. Alfred Hardisty Sellers
1907-1988

Dr. A.H. Sellers passed away in Toronto on March 6, 1988, at the age of 80, after an illness of few months.

"Alf" was born in Toronto on August 25, 1907 and received his secondary school education at North Toronto Collegiate Institute from which he graduated in 1925. He then enrolled in the combined course in arts and medicine at the University of Toronto, graduating with honors from Trinity College in 1929, and in medicine with honors in 1932. He was the recipient of three university entrance scholarships, five scholarships and prizes while at university and two postgraduate fellowships. In 1933 he was awarded the Diploma of Public Health from the School of Hygiene of the University of Toronto and later became a Certified Specialist in Public Health and a Fellow of the Royal College of Physicians and Surgeons of Canada.

He became associated with the Department of Epidemiology and Biometrics at the University of Toronto and was appointed, in 1936, the first medical statistician of the Department of Health for Ontario.

In 1940, Dr. Sellers joined the Royal Canadian Air Force where he developed "from scratch" the medical records and statistical section for the RCAF and initiated and developed the Central Statistical Bureau. He retired from the RCAF in 1946 with the rank of Group Captain, but continued his association as a consultant.

He returned to the Ontario Department of Health in 1946 as medical statistician and director of the Medical Statistics Branch and, while continuing these responsibilities, became medical statistician to the Ontario Cancer Treatment and Research Foundation in 1948 and developed the records system used by the Foundation's regional centres. He organized and was chairman of the Foundation's Committee on Records and Statistics and was a member of its Advisory Medical Board and several committees.

The statistical presentations of Dr. Sellers and his associates were important features of the Foundation's clinical conferences and of its annual reports, which later became the journal *Cancer in Ontario*. With the transfer of the Cancer Statistics Unit from the Ministry of Health to the Foundation in 1970, Dr. Sellers joined the full-time staff of the Foundation as medical statistician. Then, with Dr. W.R. Bruce and others, he organized a series of epidemiological seminars, which have been enthusiastically received by epidemiologists in Ontario and many clinicians and research workers.

Dr. Sellers retired from the Foundation in 1977, but later agreed to compile the history of the Foundation, jointly with Mr. J.H. Broughton. Dr. Sellers was responsible for describing the history of cancer control in Ontario leading up to the incorporation of the Foundation and the development of the Foundation's records and statistics program.

Dr. Sellers lent his talents to many other organizations. For many years he was active in the Canadian Public Health Association, becoming an Honorary Life Member in 1975. He continued his association with the University of Toronto as special lecturer in epidemiology and biostatistics until 1975.

For many years, Dr. Sellers was active in international organizations dealing with cancer statistics. For more than 20 years he was a member of or consultant to the Committee on Clinical Stage Classification and Applied Statistics of the International Union Against Cancer and, in 1978, received the Award of Merit from that organization in Buenos Aires for his leadership in the development of the TNM system for the classification of tumors. He was also associated with the American Joint Committee for Cancer Staging and End Results Reporting and was a member of the International Commission for Stage-Grouping and the Presentation of Results of Treatment of the International Congress of Radiology.

In 1943, Dr. Sellers was awarded the Medal of the Professional Institute of the Civil Service of Canada for his report on hospitals and hospitalization in Ontario.

In 1975, he was made a Life Member of the Ontario Medical Association.

A perfectionist and a hard worker, he was meticulous in all his activities and was the author or co-author of 144 scientific papers.

Dr. Sellers was an ardent stamp collector and an enthusiastic fisherman. He spent his summers on Manitoulin Island.

Dr. Sellers is survived by his widow Pat, and by two sons, two daughters and ten grandchildren. He will be greatly missed and fondly remembered by his many relatives, friends and colleagues.

J.H. Broughton

EDUCATION

SUMMARY OF OCTRF EDUCATION ACTIVITIES

The Foundation and the Canadian Cancer Society Ontario Division will be reviewing their respective participation in health professional and public education with the intent of improving the co-ordination of educational activities. The professional education programs for 1988 were as follows.

Postgraduate Medical Education

In 1988 the Foundation continued its support of postgraduate medical education by funding up to 20 residencies and fellowships in oncology (medical or radiation) at an annual cost of approximately $800,000. The residency posts, which supplement those funded by the Ministry of Health in the five medical schools in the province, are an attempt to relieve the serious manpower shortage in these specialties.

Undergraduate Medical Education

Ivan H. Smith Memorial Studentships

This program, jointly funded by the Canadian Cancer Society Ontario Division and the Foundation, provided 23 studentships for periods of from 4 to 12 weeks. Competition for the studentships is open to medical students after their second year of study. At the regional cancer centres and the Princess Margaret Hospital, the Ivan Smith students are introduced to the rewarding aspects of a career in oncology. In 1988, all studentships were taken outside of the academic year except for one elective. Participating centres were: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, Windsor and the Princess Margaret Hospital.

The Harold E. Johns Summer Studentships in Medical Physics

In 1988, 12 studentships were taken in the following centres: Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview and the Princess Margaret Hospital. This program, which is intended to stimulate the entry of medical physicists into oncology, is funded from a special cancer services improvement grant from the Canadian Cancer Society Ontario Division.

Continuing Medical Education

In 1988, staff members supported clinic days, seminars and guest lectures in the regional cancer centres and the Princess Margaret Hospital and gave lectures in the community. On October 28, 1988, with Foundation support, the Princess Margaret

Hospital presented a Breast Cancer Symposium at the Four Seasons Hotel, Toronto.

Last year, the pilot "phone-in" Cancer Information Service (a joint program of the Canadian Cancer Society Ontario Division and the Foundation) was expanded to cover the province. Because health promotion is an aspect of this program, we are seeking research grants to support two studies; one in smoking cessation, and the other related to education for multicultural groups. In the not-too-distant future, we hope to achieve an average of 1000 telephone calls per month, now that advertising of the service is in "full gear".

The Harold G. Vail Visiting Professorship Fund supported several lectures in the Ottawa area. On January 26, 1988, at the Ottawa Regional Cancer Centre, Dr. J. Mazeron, radiation oncologist, Hospital Mondor, Creteil, France, spoke on Interstitial Iridium 192 in Head and Neck Carcinoma. On July 7, 1988, at the Ottawa Centre, Dr. Catherine Luk, Postdoctoral Fellow, Department of Medical Biophysics, University of Toronto addressed oncologists and basic scientists on the topic "Adriamycin Sensitivity after Transient Hypoxia in Human and Mouse Tumor Cell Lines". Finally, on October 21, 1988 at the 8th Ottawa-Hull Regional Gynecological Oncology Conference held at the Ottawa Skyline Hotel, Dr. Barry Rosen, Assistant Professor of Gynecology and Oncology, University of Toronto, lectured on the subject "Ovarian Cancer: What the Obstetrician/Gynecologist Should Know".

In Ottawa, in September 1988, during the Annual Meeting of the Canadian Oncology Society, Dr. Charles M. Balch, Department of General Surgery, M.D. Anderson Hospital and Tumor Institute, Houston, Texas, delivered the W.G. Cosbie Lecture. His subject was "The Management of Melanoma - Present and Future".

The 1988 visitor selected under the Joseph J. Schiffer Exchange Program was Dr. William Duncan, Chief, Department of Radiation Oncology, Princess Margaret Hospital, Toronto. This program, sponsored jointly by Mount Sinai Hospital and the Foundation, promotes scientific interchange between Israel and the Toronto Health Sciences Centre by supporting annual exchange visits (in alternate years) of individuals working in the field of cancer treatment and/or research.

In 1988, there were two Ontario Cancer Foundation lectures. On June 17, at a meeting of the Network of Social Workers in Oncology at Queensway General Hospital, Arthur Schafer, Director, Centre for Professional and Applied Ethics, Faculty of Medicine, University College, University of Manitoba, spoke on "The Ethical Dilemma in Oncology Social Work". In Toronto, in September, at the annual meeting of the Association of Pathologists, Dr. Julie A. Righter, Head of Medical Microbiology, Toronto East General Hospital, spoke on "Antimicrobial Susceptibility Testing Methods and Reporting Policies: The Right Answer is Vital for the Patient with a Malignancy".

Dr. Cornelia Baines, Epidemiologist and Assistant Professor, Department of Preventative Medicine and Biostatistics, University of Toronto, delivered an address on "Screening for Breast Cancer in Primary Care" to the Preventative Medicine Section of the College of Family Physicians of Canada (Ontario Chapter) at its 26th

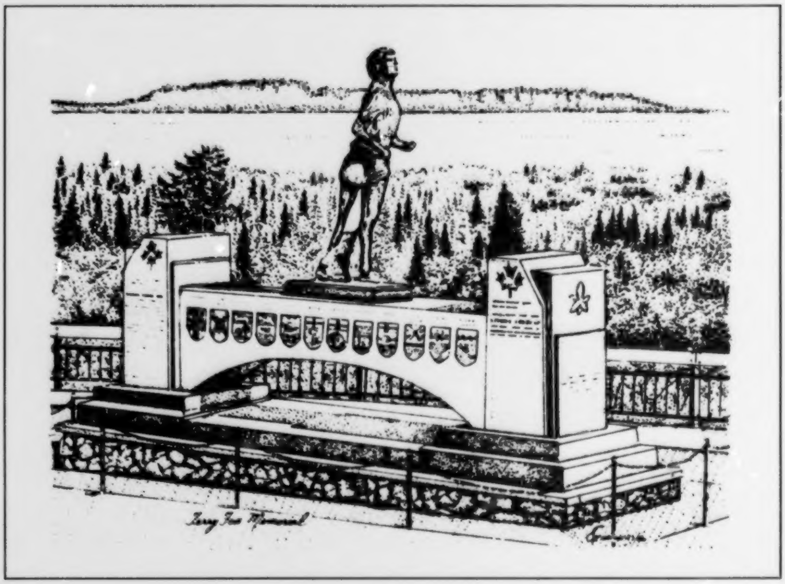
Annual Scientific and Business Meeting at the Harbour Castle Westin Hotel in Toronto between November 30 and December 3, 1988. This address was supported by a grant-in-aid.

On May 12-13, 1988, Prof. Rodney Withers, Department of Radiation Oncology, University of California at Los Angeles gave the Bert MacLaren Lecture at Henderson General Hospital in Hamilton on two topics: "Accelerated Growth of Tumors During Cytotoxic Therapy" and "Radiobiology Concepts in Everyday Practice". On September 16, 1988 at Lakehead University, Thunder Bay, Dr. Kerstin Sjoval, Department of Gynecological Oncology, Radiumhemmet, Karolinska Hospital and Institute, Stockholm, Sweden, delivered another Bert MacLaren Lecture on "Early Diagnosis of Ovarian Cancer" during the 25th OCTRF Clinical Conference.

Mary Lou Erochko
J.C. Laidlaw, M.D.

25TH OCTRF CLINICAL CONFERENCE

EARLY CANCER: DETECTION AND MANAGEMENT



Terry Fox Memorial

The 25th Clinical Conference, held at Lakehead University in Thunder Bay on September 16, 1988, examined the possibilities for early diagnosis in three of the common female cancers. Dr. A.B. Miller (University of Toronto) and Dr. E.A. Clarke (OCTRF) talked on early detection and screening of carcinoma of breast and cervix, and Dr. K. Sjövall (Karolinska Institute, Stockholm, Sweden) discussed early diagnosis of carcinoma of ovary. These diagnostic sessions were followed by descriptions of the options we have for effective treatment of those early lesions. Dr. A. Recht (Harvard Medical School) and Dr. C.K. Osborne (University of Texas) spoke on therapy of early carcinoma of breast. Dr. G. O'Connell (Hamilton Centre) discussed management of premalignant and early malignant lesions in carcinoma of cervix. Treatment of carcinoma of ovary was discussed by a surgeon, Dr. J. Carmichael (Queen's University), radiation oncologist, Dr. A. Dembo (Toronto-Bayview Centre), and medical oncologist, Dr. L. Levin (London Centre). Dr. E. Sondik, from the National Cancer Institute of the United States, was unable to reach the conference site in time but forwarded his manuscript for the proceedings. In his place, Dr. A.B. Miller discussed the impact of early detection on cancer control. In his closing remarks, Dr. J.W. Meakin pointed out that this conference signals the increased attention the Foundation is paying to early cancer detection and prevention. The conference was attended by more than 150 participants. The following summaries include data presented at the conference.

Participants at the conference, back row: Drs. M. McLean, A. Recht, G. O'Connell, A.B. Miller, L. Levin and E.A. Clarke; front row: J.F. Kotalik, J. Carmichael, J.W. Meakin, V. Basrur, A. Dembo and C.K. Osborne.

EDITORIAL: SCREENING FOR CANCER IN ONTARIO

Thirty years ago the United States Commission on Chronic Illness defined screening as "...the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures, which can be applied rapidly to sort out apparently well persons who probably do have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred for diagnosis and necessary treatment."

It is most encouraging that, as described elsewhere in this issue, screening has been shown to be effective in reducing the morbidity and mortality from cervical cancer and breast cancer, two of the most common cancers in women. Screening for cervical cancer using the "Pap" smear has been practised in North America for many years but, as has been shown, maximum benefit is achieved in those jurisdictions with organized programs such as Finland, Iceland and Northeastern Scotland. The essential elements of organized screening programs are:

- the identification of individual women in the target population, using measures that ensure high coverage and attendance, such as a personal letter of invitation;
- adequate facilities for screening and for the diagnosis and management of abnormalities;
- an organized program of quality control; and
- the evaluation and monitoring of the program in terms of the incidence and mortality of the disease for which the screening program was introduced.

In this province it is not yet evident whether we can achieve the maximum gain from screening for breast cancer using mammography, with or without physical examination and for cervical cancer using the Pap smear. Several possible reasons for this uncertainty are discussed below.

Historically, new approaches to the delivery of health care have been regarded as controversial. When Jenner informed the world that he could prevent smallpox by vaccinating people with cowpox, he was denounced as a "beast of the apocalypse". Semmelweiss who, before Lister and Pasteur, was able to reduce mortality from puerperal fever by persuading fellow physicians to wash their hands before examining women in labor, died in poverty and disgrace.

On a milder note, the current medical and public literature is undecided about the value of these screening tests. Some authors assert that screening is valuable for both breast and cervical cancer while others say that screening does more harm than good and that it is unethical to apply screening tests to healthy women. Also the literature is contradictory concerning the age at which screening should start and the frequency with which women should be screened. Thus many practising physicians are undecided about who should be screened and when they should be screened. The appropriate government departments, health agencies, the scientific community should establish clear guidelines. We should then make all women aware of these guidelines so that they may make informed decisions about their health. These decisions are made best within the context of an organized program.

Organized screening programs incorporating the elements identified by Hakama would represent a new approach to the delivery of health care in Ontario. The concept is controversial and not many individuals understand why opportunistic screening can never be as successful as organized screening.

All successful screening programs have made a positive effort to recruit women into the system. Older women are at a higher risk of developing breast cancer and cervical cancer than young women and therefore benefit most from screening. However, many studies have shown that older women present themselves for screening less frequently. Also they may neglect or refuse screening because they do not believe that they will get the disease, because they are afraid of the implications of the positive test, because they are embarrassed by the procedure, or simply because they are apathetic. Health promotion efforts are essential to overcome these barriers. More women will come forward when they are individually identified and sent a personal invitation to the program.

Once they enter a program, it must ensure adequate follow-up of abnormal findings detected at the screening; this is essential to minimize anxiety by efforts directed at the prompt diagnosis of the abnormality and the delivery of appropriate treatment.

The program must incorporate a "current best" method of treating the diagnosed abnormalities. Unfortunately, there is no concensus concerning the management of the lesions found by early detection in both these cancers. For example, should women with Stage I, node-negative cancer, receive adjuvant therapy? Should the lesion be treated by simple excision or should the excision be followed by chemo- or hormonal therapy? We are uncertain whether all women with precursor lesions of invasive cancer of the cervix, in particular cervix intraepithelial neoplasia, class I and II, should be referred for colposcopy. We do not know whether all such lesions will progress to invasive cancer or whether some are manifestations of infections with human papillomavirus.

If organized screening programs are introduced into Ontario, they must be planned and undertaken with care and with appropriate evaluation to ensure their effectiveness. Without such efforts, which will require commitment from all concerned, women will continue to die unnecessarily from breast cancer and cervical cancer.

E.A. Clarke, M.B., B.S., M.Sc.
Head
Division of Epidemiology and Statistics

EARLY DETECTION OF BREAST CANCER*

A.B. MILLER, M.B.,Ch.B.**, *Toronto, Ontario*

Effectiveness of screening has been established for only two cancer sites -- breast and cervix uteri. Only for these, therefore, should screening be considered as part of routine clinical practice. The effectiveness of screening will depend on the extent to which eligible women are screened, thus it is essential to have mechanisms that ensure that all eligible women are screened. For cancer of the breast, current evidence justifies only screening from the age of 50, continuing at least to the age of 70. Mammography every two years will provide nearly maximal efficacy. Although the contribution of breast self examination and physical examination of the breasts remains to be determined probably one should apply these measures in all women from the age of 40. Because of organizational and other difficulties, it seems unlikely that screening will make a major contribution to reduction in overall cancer mortality by the year 2000. However, if we can overcome certain organizational problems, screening could make a major contribution to reduction in breast cancer mortality.

This paper will discuss some of the issues relating to the application of screening for cancer and summarize the state of the art in screening for cancer of the breast.

What is screening?

Screening is the process designed to detect disease earlier in its natural history than occurs in normal clinical practice. Some authorities make a distinction between case finding -- the application of tests in a physician's office as part of an encounter initiated for another purpose, and mass screening -- the administration of tests to the whole population, or a substantial proportion of the whole. This distinction has become blurred because usually many tests, such as a physical examination of the breasts, are administered in a physician's office, yet we should apply the same criteria for their application as for such tests as mammography administered from special centres. Also, the same ethical principles should apply in both circumstances, namely the test must be effective and as free from hazard as possible, because those eligible for screening usually will be healthy and without symptoms. Any hazard associated with the test will affect large numbers, whereas benefits usually will accrue only to a few of those tested.

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* Abstract of a paper presented at the 25th OCTRF Clinical Conference held at Lakehead University, Thunder Bay, September 16, 1988.

** Professor, Department of Preventive Medicine and Biostatistics, University of Toronto.

How do we decide when screening is effective?

Evaluation can be considered in terms of the screening test, and the programs into which the test is incorporated. A screening test should be valid (i.e. of adequate sensitivity) in the circumstances of its use. Sensitivity -- the ability of a test to detect disease, is expressed as the proportion of those who have detectable disease who test positive. Specificity -- the ability of the test to exclude disease, is expressed as the proportion of those free of the disease who test negative. The demonstration of case-detection ability, however, is not sufficient to justify introducing screening into practice; before he does that, its proponent must confirm that application of the test will reduce the incidence and/or the mortality from the disease. Such confirmation requires that we evaluate the effectiveness of screening programs.

The UICC project[1] concluded that the most effective way to evaluate the effectiveness of screening programs was by randomized controlled trials. In practice this means that valid screening tests should be incorporated into a screening program, and the program evaluated by means of a controlled trial. Trials of screening require a major investment in resources and furthermore one cannot evaluate all aspects of screening in this way. However, such a large investment is required to screen the general population, even if restricted to certain age groups, that we should not permit any compromise on the principle that the general introduction of screening should be preceded by a controlled trial to establish the effectiveness of screening.

Usually physicians assess the outcome of cancer treatment by comparisons of survival. However, the potential effect of screening biases are so great that we cannot rely on assumptions of effectiveness based on improved case survival. The principle biases are those of: lead time, length, selection and overdiagnosis. Lead time is the extent by which diagnosis is advanced by the screening test. Length bias is the tendency for intermittent screening to detect the slow-growing cancers and to miss the rapidly progressive cancers. Selection bias refers to the fact that health-conscious women tend to participate in screening programs. Overdiagnosis bias is the fact that some screening tests will pick up lesions that might never have presented in the woman in the absence of screening. This may occur during mammography. Thus, one can determine the effectiveness of screening only by reduction in mortality (deaths applied to the whole population rather than the cases).

Even after deciding to extend a program to the general population, we are obligated to monitor the program to confirm its continuing effectiveness, bearing in mind that primary prevention could make screening less cost-effective, while improvements in therapy of clinically detected disease might make screening unnecessary.

Screening for breast cancer

Screening for breast cancer can reduce mortality from the disease[2], as shown by two completed randomized trials[3,4] and three case-control studies[5-7]. Of these, only one, the Health Insurance Plan (HIP) trial, showed that it was effective in women age 40-49, and only on prolonged follow-up[3]. All, however, showed effectiveness in women age 50 or more.

The HIP trial and the Utrecht study combined mammography and physical examination. The other studies were based on mammography alone, though in the Swedish trial, the screening process incorporated a visual examination of the breasts. Also the women received a pamphlet explaining breast self examination (BSE) and advising them to practice the technique. Single-view mammography was used in the Swedish trial (medio-lateral oblique) and in Nijmegen (lateral). The other studies used double-view. Initially Utrecht used xerography but it changed to film-screen in 1980. All other studies used film (HIP) or film-screen. Screening was annual only in the HIP study. In Utrecht the intervals were 18 months, 2 years, and then 4 years; in Nijmegen, screening was biennial; in Florence[7] every 2 1/2 years; in Sweden every 21 months in women age 40-49, every 33 months in older women. Studies that used a long interval between screens provide indirect evidence on the optimal frequency of rescreening; from these, one can determine the proportion of the expected incidence of breast cancer (measured in the control group or from other data), which presents in the interval between screens. The Swedish[8] and Nijmegen[9] studies indicate that screening every two years is satisfactory in women over the age of 50, but that younger women would require annual screening programs.

All the studies had a similar order of effectiveness, approximately a 40% reduction in breast cancer mortality in women age 50 or more at 5 (HIP) to 7 (Sweden) years after initiating screening. Clearly this order of effectiveness can be achieved by mammography alone; however, the Canadian National Breast Screening Study (NBSS)[10] hopes to determine whether physical examination (and BSE) provides most of the benefit in the combination with mammography, or can be substituted for mammography.

Although final results from the NBSS will not be available for some years, NBSS does have data on detection of breast cancer, and on early mortality from this lesion. The breast cancer mortality experience is complete only for the first three years following entry, but life tables can be used to extend the curves to five years. Thus one can compare these figures with survival data from the HIP study and from the U.S. Breast Cancer Detection Demonstration Project (BCDDP)[11]. Comparing the first 3 years of NBSS experience with HIP data suggests a similar relationship of deaths to diagnosed cases in the women age 50-59, but a much improved survival in women age 40-49. This conclusion is like that reported for the BCDDP and Seidman et al believe this is evidence that modern screening is effective in women age 40-49[11]. However, in this age group, the NBSS control group survival is at least as good as the screened group. Therefore, such survival data cannot be used to indicate a benefit from screening, rather it indicates the effect of self-selection for screening, and/or the effect of improvement in (short-term) survival from adjuvant chemotherapy.

Thus we may conclude that both single-view mammography alone and double-view mammography combined with physical examination reduce mortality from breast cancer. Current data are insufficient to determine whether we would derive appreciable extra benefit (in terms of mortality reduction) from adding physical examination to mammography, or from double-view as distinct from single-view mammography. Further it is not clear whether mammography adds appreciable extra benefit to screening by physical examination--this possibility is being investigated in the NBSS in women age 50-59 on entry to the study[10]. It is important to find answers to these questions because of the high cost of mammography.

So far only the HIP has suggested that screening is effective in women age 40-49. However, even if one assumes this benefit, the calculations of Eddy et al[12] suggest that for women of this age group screening will not be cost effective. Although none of the projects using more modern mammography have reached the point in follow-up where the HIP study began to show apparent benefit in younger women, these projects have lasted long enough to confirm that, even if this screening produces benefit in younger women, eventually it will be delayed compared to women over the age of 50. We have no explanation for this age difference to time of significant effect but it may be due to relatively poorer sensitivity of the screen.

Also as yet we have no evidence concerning the effectiveness of BSE, but several studies now ongoing may provide such evidence[2]. Clearly only BSE has the potential to improve the outlook for interval cancers, while its teaching probably has diminished false reassurance in the NBSS. The World Health Organization concludes that in many parts of the world only BSE has the potential to provide early diagnosis of breast cancer[13]. However, we may have to wait 10 years or more before we learn whether this potential is real or illusory.

The UICC project, as others[14,15] did, emphasised the importance of high-quality mammography and of the skills needed to localize and diagnose the impalpable lesions found on mammography. The NBSS has demonstrated that, using films of adequate contrast and definition, high quality requires constant attention to the details of positioning and compression, film type and screen, darkrooms, development of film, as well as kilovoltage, phototiming and dosage. These aspects were supervised by a reference physicist. Also, we had a reference radiologist, who assessed the performance of the radiologists reading the films.

Given available scientific evidence, what should we tell an individual woman about breast cancer screening, and how should her physician advise her?

First, the certainties:

1. The only risks in screening are those of unnecessary biopsy and false reassurance. In North America only about 1 in 5 of the biopsies performed as a result of screening reveal cancer. Eventually, with improved diagnostic abilities, this will be reduced to the 1 in 2 claimed in the best Swedish centers; however, our medicolegal system probably will keep the ratio higher (usually, when in doubt, the doctor concludes that it is safer to biopsy than to wait). False reassurance is minimized when women and their physicians realise that interval cancers -- those that develop between screens after a negative screen -- appear at about the rate of 1 per 1000. One of the main justifications of BSE is that it finds these cancers early. Modern mammography is safe. Also, in the age group for whom screening normally is considered (age 40 or more), the risk of radiation-induced breast cancer is negligible.

2. All women age 50 or more should be screened regularly. Although the standard recommendation is annual mammography and physical examination, evidence from European studies supports the efficacy of screening with mammography every 2 years.

3. Mammography should be of high quality, conducted by a group with experience with screening. High quality does not equate with high cost. An experienced group with the necessary volume to ensure quality control will not need to charge $100 or more to make a reasonable profit. One-half of that is more than enough. Anyone who charges $100 or more probably operates a service of such a low volume that one has good grounds to doubt their efficiency and experience.

Now, the controversies:

1. In my opinion, we do not have enough evidence to recommend screening for women age 40-49, and none to recomend screening at an earlier age, even for those judged to be at high risk. However, it is possible that eventually women under the age of 50 will be shown to benefit. Breast cancer is a disease with a long natural history. Many women who develop breast cancer in their forties die of it in their fifties. Screening does not seem to prevent the deaths from breast cancer in women in their forties after the diagnosis has been made in their forties. However, it may help women in this age group who have cancers with a longer natural history. Thus it is a matter of individual physician judgement whether to incur the costs now in the hope of a benefit later, or because the probability of benefit is low, to delay screening until a woman's 50th birthday.

2. What about physical examination and BSE? There is no clear evidence in favor of either, although, in the NBSS, both contributed to the early detection of breast cancer. In the HIP study, physical examination contributed substantially to such detection, especially in women age 40-49; indeed it seems likely that physical examination made the greatest contribution to the reduction in breast cancer mortality. In our hands, the costs were low, about $12 for a physical examination by a specially trained nurse, who also taught BSE. The examination requires care because the signs of early breast cancer are much different from those of the advanced disease -- the technique usually taught physicians[16]. As a useful compromise for screening women age 40-49, one might propose an annual physical examination, and the practice of BSE -- assuming that the woman has the necessary skills. For women age 50 or more, annual physical examination by a skilled professional *plus* the teaching and reinforcement of BSE may achieve nearly all the benefits provided by the combination of physical examination and BSE with mammography. At least in the short term, this group of services is what is being provided in the NBSS. Only time will tell what range of services will prove to be best in the long term. In the meantime, as Clarke has described elsewhere, many believe that new programs should incorporate all three modalities. Others, including myself, have suggested that we wait for the results from the NBSS before embarking on expensive, population-based mammography programs. Government policy-makers will have to choose the best available program in the light of competing demands on health-care

resources, while individual women and their physicians will try and make the best decision in the light of their assessment of the evidence.

3. Whether women perceived to be at high risk should receive special consideration depends on the degree of risk, and the woman's anxiety over it. The only woman at high risk is the rare individual under the age of 50, who gives a positive family history of premenopausal breast cancer in a first-degree relative (mother and/or sister). Such a person might wish to add mammography to physical examination and BSE; if so, it should preferably be annual.

4. When do we stop screening older women? In North America the risk of developing breast cancer increases throughout life, therefore it scarcely seems logical to stop screening at age 65 or 69. In the screening studies, the upper age limit ranged from 64 to 74 on entry. The HIP[3] and the Nijmegen[6] studies gave some indication that screening was less effective in women age 60 or more than in women age 50-59. The Utrecht study showed the reverse[5]. In the Swedish trial[4], screening was as effective in women age 60-69 as in women age 50-59, but was less effective in women age 70-74. Although this trial included older women, its compliance with invitations to attend for screening was poor and the results were not analysed. Perhaps this gives a clue to policy. If women are prepared to be screened in their seventies, they should be encouraged to do so. However, if they have more pressing health problems, we might dispense with screening but continue with BSE and regular physical examinations.

Prospects for the future

Before screening can make a major contribution to cancer control, we must overcome a number of obstacles. These include an unfavorable natural history of many cancers, poor organization of screening programs, non-availability of a valid and effective screening test, and poor compliance of those at risk, sometimes exacerbated by economic barriers -- as in mammography for breast cancer.

The contribution of screening to a reduction in cancer mortality is potentially important, but is not dramatic. However, we must regard even the degree of mortality reduction achieved by breast cancer screening as temporary palliation, because for continued effect, screening programs must be continued indefinitely. Thus screening is a less productive approach to the control of cancer than primary prevention -- although the latter may require many decades to achieve its full potential. Pending this, screening, which offers a fairly rapid return from appropriate investment, should remain part of our program for cancer control.

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CARCINOMA OF THE BREAST: SCREENING IN ONTARIO*

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As described elsewhere in this issue by Miller, screening asymptomatic women to detect breast cancer in its early stage currently is the only method of controlling this cancer. In three randomized clinical trials and four other studies of a number of screening tests, only mammography, either alone or in combination with physical examination, has been shown to decrease mortality from breast cancer.

Screening to reduce breast cancer mortality confers a significant potential benefit to many women in Ontario. The Ontario death rate for this cancer, adjusted for age, is among the highest in North America and Europe; this rate has remained almost unchanged for more than 50 years, despite the introduction of new treatments such as adjuvant chemotherapy and hormonal therapy. With the increasing size and age of Ontario's population in the last 20 years, the burden of this disease also has increased; the number of deaths almost has doubled -- from 945 in 1968 to 1708 in 1987.

Neoplasms of the breast are the most common form of cancer in Ontario women, excluding non-melanotic cancer of the skin which is rarely fatal. Breast cancer is both the leading cause of death and of premature deaths from cancer in Ontario women. The average Ontario woman has a 1 in 10 chance of developing breast cancer in her lifetime. In Ontario, as in Denmark[1] and the United States[2], the incidence of breast cancer increased in recent years, rising from 65.1 in 1980 to 71.0 per 100,000 women in 1986. As a result, 849 more women were diagnosed as having breast cancer in 1986 than in 1980. Thus, breast cancer is a major public health problem in the Province and for this reason we must take advantage of the scientifically established fact that screening for breast cancer is the only widely accepted method of reducing deaths from this disease.

Following review of the published studies on the effectiveness of screening from the United States and Europe, population-based, organized breast cancer screening programs are being implemented in Finland, Iceland, the Netherlands, Sweden and the United Kingdom. Also, pilot projects are being undertaken in some jurisdictions, e.g., British Columbia and Australia.

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After the closure of the five National Breast Screening Study[1] (NBSS) centres in Ontario in 1987 and 1988, the Board of the Ontario Cancer Treatment and Research Foundation (OCTRF) decided that the technical expertise and staff experience established in these centres should be maintained. Also that in Ontario a mechanism should be developed to implement a program of breast cancer screening that would reach all women who would benefit. In this regard on July 30, 1987, the Minister of Health, Mr. Murray Elston, met with representatives of the OCTRF and, on August 25, 1987, Mr. Elston wrote to Mr. M.A. Meighen, Chairman of the OCTRF Board, asking the OCTRF to design and develop a proposal for a province-wide, integrated, comprehensive Breast Cancer Screening Program ('The Proposal'). This proposal has been prepared and submitted to the Minister of Health for Ontario. When fully implemented, this program aims to reduce by 40% the mortality from breast cancer in Ontario women over the age of 50 by screening at least 70% of women in the appropriate age group. Such screening would save more than 300 lives each year.

The Proposal recommends two screening modalities, namely double-view (mediolateral oblique and craniocaudal views) film-screen mammography and physical examination by a trained nurse-examiner. Based on a recent update of the Swedish two-county study[4], women will be screened every two years.

Three factors determine the age group to be included in the program: effectiveness; compliance; and person-years saved at different ages. These considerations must be tempered by two others -- the frequency of re-screening and the age to stop screening.

All studies to date have shown that compliance with invitations to attend screening decreases with increasing age. In the Swedish two-county trial[5], compliance was so low in women over the age of 74 that the study could publish no results for such women. In older women, screening saves fewer person-years because of competing causes of death, although this is compensated to some extent by the increase in breast cancer mortality with increasing age.

There is considerable controversy in North America regarding the risk and benefits of screening women under age 50. An 18-year follow-up of the participants in the Health Insurance Plan (HIP) of Greater New York study[6] demonstrated a 25% decrease in mortality in women under age 50. However this result has been questioned on several counts, including the small number of patients involved, analysis by age at diagnosis, as opposed to age at entry, and biologic implausibility. Others have criticized a subsequent second analysis of the data from the HIP study[7] which included cancers identified after the end of the study. Also case-control study in Florence, Italy[8], demonstrated a reduction in mortality in women under age 50, which was not significant. Although the Breast Cancer Detection and Demonstration Project[9] showed no difference in survival between women screened under age 50 and those over age 50, it is difficult to estimate the reduction in mortality as a result of screening because of the absence of controls.

On the other hand, the Malmo, Sweden[10] and the Swedish two-county[5] randomized clinical trials both showed no benefit of screening in younger women; indeed, there were more deaths from breast cancer among the younger women who were screened. Also, a case-control study in Nijmegen, Netherlands[11], showed an excess mortality in younger women. The Swedish two-county trial[4] showed that the accuracy of mammography in identifying cancer was only 60% in women age 40-49 years, compared with 85% in women age 50 years and above.

The lack of effectiveness of screening in women under 50 has been attributed to several factors: the hypothesis that breast cancer in younger women is a different disease with a different biology; that it is more aggressive; and that it may be detected only by more frequent screening; (a negative "screen" in younger women may have falsely reassured some of these patients and caused a dangerous delay in diagnosis). In addition, frequently young women have dense breasts and, in this circumstance, mammograms are more difficult to interpret.

It is a basic public health principle to target those groups that will benefit most from a program. Thus, with limited health care resources, an initial province-wide program should target those women who will receive the greatest benefit, with the option to extend the age range once the results are available of studies in progress and the success of the program is known.

Table I gives the age distribution of the female population in Ontario, with the number of new cases and the number of deaths from breast cancer for 1986, the most recent year for which there is incidence data. In view of the conflicting evidence concerning the effectiveness of screening in women under age 50, the fewer number of detected cases and deaths in younger women and the large number of women in the under-50 age group, the proposal recommends that the initial target group be women aged 50-64. Women will be retained in the program until their 70th birthday when screening will be discontinued. As women reach the age of 50, they will be invited to attend for screening. Thus, over a six-year period, the ages covered by the program will enlarge from 50-64 to 50-69. In the future, if resources permit and there is evidence that screening is effective for younger women, the lower age limit could become 45 or 40. The upper age limit could be raised to 74 years, if additional resources become available and women in their late 60s show good compliance.

The proposed screening program for Ontario is based on the essential elements Hakama et al described in 1985[12], namely:

- the identification of individual women in the target population with measures to ensure high coverage and attendance, such as a personal letter of invitation;
- adequate facilities for screening and for the diagnosis and management of abnormalities;
- an organized quality-control program;
- the evaluation and monitoring of the total program in terms of the incidence and mortality from the disease for which screening was introduced.

TABLE I

Breast Cancer Incidence and Mortality
Ontario 1986

Age Group	Number of New Cases	(%) of New Cases	Number of Deaths	(%) of Total Deaths	Population*
<40	328	7.5	86	5.1	2,828,000
40-44	350	8.0	79	4.7	292,300
45-49	367	8.4	109	6.5	244,100
50-54	436	10.0	162	9.6	230,100
55-59	489	11.2	179	10.6	229,700
60-64	543	12.4	238	14.0	227,900
65-69	527	12.0	171	10.1	181,900
70-74	488	11.1	194	11.5	150,800
75+	839	19.1	471	27.9	249,100
Unknown	11	0.3	–	–	–
TOTAL	4,378	100.0	1,689	100.0	4,633,900

*Population figure given to the nearest hundred.

Women in the target age group will be identified through the Ministry of Revenue, which has agreed to provide the OCTRF with a computer tape from the Ontario tax assessment rolls providing names, addresses and postal codes of all women between age 50 and 69, with the understanding that certain provisions will be maintained regarding privacy and confidentiality. Later, these data may be replaced by other sources, such as a population-based register, as exists in other countries.

Women will be referred for screening to a centre associated with the program by their attending physician, will be self-referred or will be invited to attend by personal letter.

For health professionals and the public, the OCTRF will develop a health-promotion strategy to ensure that 70% of women in the target population attend for screening. When fully operational, the program will screen 305,000 women per year.

To ensure adequate facilities for diagnosis and treatment, it is proposed to establish dedicated screening centres associated with the Regional Cancer Centres of the OCTRF. Each of these centres will be administratively responsible for additional centres. Dedicated centres will be equipped and staffed to screen up to 10,000 women per year. The number of additional centres will be determined by the size and density of the population of women in the target age group in the region served by the centre.

The requirements of Ontario's large population can be met only through optimum utilization of the human skills and technical equipment already in the Province. Existing screening facilities in hospitals or private radiology practices may wish to participate in the organized provincial program by becoming affiliated centres. Accreditation of such facilities will depend on their ability to meet prescribed standards, their willingness to participate in quality-control and peer-review programs and their agreement to provide data for ongoing evaluation.

The program, which will be organized and administered by the OCTRF, will be designed to ensure adequate facilities for the diagnosis and management of abnormalities detected at the time of screening. Quality control measures will be introduced and maintained. The program will be monitored and evaluation will include such parameters as the number of cancers detected in screened and unscreened women, the occurrence of interval cancers, survival and deaths from breast cancer.

These recommendations for screening in Ontario are similar to those developed by a workshop convened on March 16-17, 1988 to develop a Canadian approach to the early detection of breast cancer. This workshop was sponsored by Health and Welfare Canada, the Canadian Cancer Society and the National Cancer Institute of Canada, on behalf of the Conference of Federal-Provincial Deputy Ministers of Health.

In its report, the workshop recommended "....that Canadian women aged 50 to 69 be offered and encouraged to participate in an early detection program consisting of mammography, physical examination of the breasts by a health professional, and teaching and monitoring of breast self-examination every two years. This should be done through dedicated screening centres." These recommendations have been endorsed by the Canadian Cancer Society and accepted by the Federal-Provincial Deputy Ministers of Health; at their request, the report is to be published and widely disseminated. It should be noted that the workshop made no recommendations concerning the screening of women aged 40-49; except that this should be done at dedicated centres.

Miller and others have suggested that the establishmemt of province-wide programs for breast screening be delayed until we have the results of the NBSS. As Miller has stated elsewhere in this issue, in this study the mortality experience is complete only for the first three years following entry. In the recently published U.K. trial[13], screening centres using a combination of mammography and physical examination achieved a 40% reduction in mortality, which only became evident seven years after entry. In Malmo[10], another randomized clinical trial using mammograph gave a similar result. They observed no difference in mortality until eight years after entry but, 10 years after entry, mortality in the screened group had been reduced by 42%. Therefore, results from the NBSS may not be available for another four years, during which time there will be, according to past experience, a steady increase in the number of "spontaneous" or random mammograms done on women in this province.

In Ontario the number of mammograms has increased from 70,000 in 1983 to

155,000 in 1987, at a cost of eight million dollars. It can be assumed that using the 40,000 mammograms taken in 1979 as a baseline for diagnostic mammography, physicians ordered or performed most of these for screening purposes. In 1987, 50% of the mammograms were done on women under age 50, a group for which no benefit from screening has yet been clearly demonstrated.

Therefore, if an organized program in Ontario is not implemented until the results of the NBSS are available, many women for whom screening mammography is effective will not receive it and many younger women, who will not benefit, will be screened. Also, women may be screened at inappropriate intervals. It is expected that an increasing number of women will be referred for screening by mammography and, if the present trend continues, in the rext four years more than 300,000 mammograms will be done at a cost of 16 million dollars. It should be noted that the estimated annual operating cost of a fully developed province-wide program that will screen 305,000 women per year --70% of the target population, is the same amount -- 16 million dollars.

Eddy[14] has suggested that, without an organized program, only 30% women in the target age group would be screened. Screening such a low proportion of women would prevent only 80 deaths compared with 300 lives saved by an organized program.

The present arrangement in Ontario, "laissez-faire mammography", has no means to ensure comprehensive coverage and the attendance of older women who will benefit from screening. It incorporates no formal mechanism to ensure that women with abnormal findings are investigated and treated, no ongoing quality control of the equipment, the quality of the mammograms, their interpretations, etc. It has no means of monitoring or evaluating the results of this large expediture of professional time and scarce health-care dollars.

In conclusion, in Ontario events are overtaking us. Unless we implement an organized program of screening for breast cancer now, it will be difficult to to so when the results of the NBSS become available. By that time, screening mammography will be common practice for younger women and it will also be difficult to change established patterns of medical practice. There is no doubt that screening using mammography can reduce mortality from breast cancer. It would be tragic if Ontario were to miss this opportunity for positive action based on an intervention that modern science has tested and proved to be effective.

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ADJUVANT THERAPY ON NODE-NEGATIVE BREAST CANCER*

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Generally, initial trials of contemporary adjuvant chemotherapy in breast cancer were restricted to patients with positive axillary nodes because of their relatively high risk for distant relapse. From 10-year results of these early trials[1,2] and an overview analysis of most of the completed trials[3], one can draw the following conclusions:

1. Adjuvant chemotherapy prolongs disease -- free and overall survival.
2. Premenopausal patients show a substantial benefit, whereas in older patients this is less clear. These differences related to menopausal status may represent differences in chemotherapy dose delivered or they may be due to differences in tumor biology in younger and older patients.
3. Postmenopausal patients, especially those with estrogen receptor-positive tumors, benefit from adjuvant tamoxifen therapy, while no one has demonstrated consistently an advantage in premenopausal patients.
4. Combinations of cytotoxic drugs are superior to single agents.
5. Shorter treatment (≈6 months) appears to be as effective as longer, at least with certain regimens (i.e., CMF)[2].

We hope ongoing clinical trials will answer several important questions in node-positive patients. Preliminary data suggest that Adriamycin-based regimens have an advantage, especially in older women[4-6]. Also under investigation are chemoendocrine therapy -- cytotoxic agents combined with anti-estrogen therapy or with castration -- and questions concerning dose intensity and pre- or perioperative therapy.

When the benefits of adjuvant therapy in node-positive patients became apparent, studies were initiated of adjuvant systemic therapy in patients with lower-risk, node-negative breast cancer. In this group, studies of adjuvant therapy posed special difficulties because overall 60-70% of patients would be cured by surgery alone and would not benefit from systemic therapy. With this in mind some of these studies focused on node-negative patients at higher risk for recurrence, as defined by estrogen-receptor status of tumor size. These trials evaluated both cytotoxic chemotherapy and adjuvant hormonal therapy.

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Frequently, early trials of adjuvant therapy in node-negative patients had relatively small numbers. Furthermore, the node-negative patients usually were a subset of a larger trial focused primarily on node-positive patients. Finally, these trials used what many would consider to be sub-optimal chemotherapy[6]. Of the six trials randomizing patient to either a control arm or to chemotherapy, only one was carried out in the USA. All of these trials showed a trend in favor of chemotherapy in either disease-free or overall survival although the differences, except for the Nissen-Meyer trial of perioperative cyclophosphamide, did not reach statistical significance (Table I).

In 1986, the Milan group published early results (2-year medium follow-up) of a trial comparing "no treatment" with 9 months of intravenous CMF in node-negative patients with ER-negative tumors[7]. They observed a striking disease-free and overall survival advantage with CMF (Table II). Many have criticized this trial because of its small size (89 patients) and because the control patients had a particularly poor outcome -- a 50% recurrence rate at only 3 years.

Adjuvant hormonal therapy with tamoxifen has been studied in node-negative patients. The NATO trial included 604 postmenopausal patients randomized to tamoxifen for 2 years or no treatment[8]. Treatment gave a significant disease-free and overall survival benefit. A Scottish trial randomized 751 patients to tamoxifen for 5 years or no therapy until relapse[9]. It showed a similar advantage for tamoxifen. In contrast to most trials in node-positive patients, these studies showed that tamoxifen gave a modest benefit even in ER-negative tumors.

Recently, three other larger trials have completed accrual and, in a "clinical alert", the NCI disseminated the early results (Table III). An NSABP trial with more than 2600 patients with ER+ tumors compared tamoxifen for 5 years with no adjuvant treatment. A 4-year median follow-up showed a modest but statistically significant benefit from tamoxifen; 82% were disease-free on tamoxifen compared to 77% controls. The difference was evident in both pre- and postmenopausal patients.

In another NSABP study, 741 node-negative, ER-negative patients were randomized to no treatment or to 12 4-week cycles of methotrexate, 5-FU, and leucovorin. At 4 years, 80% of the chemotherapy group and 71% of the control group remained disease-free. Both pre and postmenopausal patients benefitted.

Another study (INT-0011), an intergroup trial including ECOG, SWOG, and CALGB, randomized 472 patients with ER-negative tumors or ER-positive tumors >3 cm in diameter to 6 cycles of CMFP or to no treatment. Patients with ER-positive small tumors were followed without adjuvant treatment. In the randomized study, at a median follow-up of 3 years, 84% of chemotherapy patients remained disease-free compared to only 67% of controls ($P = 0.0001$). Benefit was observed in ER-positive and ER-negative, as well as in pre- and postmenopausal subsets. In the registration study, 15% of patients with ER-positive small tumors had recurred.

Several points deserve emphasis. First, follow-up time is relatively short and differences now seen could change with time. Second, at the present time only the Milan, NATO and Scottish trials show a significant survival advantage. Too few have died in the other trials to provide meaningful survival data. Third, in these trials node-negative patients seem to have a poorer outcome than those in earlier trials who showed only a 30-35% recurrence rate at 10 years. This "worse prognosis" may be related to patient selection. Fourth, although the treatment regimens were tolerable for most patients, study deaths due to toxicity did occur and we do not yet know the long-term consequences of treatment in patients who are cured.

Prognostic Factors

It seems clear that node-negative patients do receive some benefit from adjuvant therapy. The challenge now is to define optimal therapies for various subsets and, importantly, to develop techniques to identify the majority of node-negative patients who are cured by surgery alone and who should not be subjected to potentially toxic systemic therapies. Although hormone-receptor status helps to distinguish prognostic subgroups, when used alone, it is not good enough. DNA flow cytometry to determine ploidy status and S-phase fraction appears promising[10]. A retrospective study of node-negative patients showed that DNA ploidy status was the most important prognostic factor -- more important than ER status or tumor size. Within the group of diploid tumors, the S-phase fraction provided additional prognostic information. At a median follow-up of 4.5 years, <10% of diploid tumors with low S-phase fraction had recurred regardless of ER or size. Aneuploid tumors or diploid tumors with a high S-phase fraction had a worse prognosis. Prospective clinical trials of these and other prognostic factors should demonstrate their importance. Before this technology becomes widely available, we will require standardization of analytical techniques in DNA-flow cytometry and laboratory quality assurance programs will be required.

Current Recommendations

Several points deserve emphasis. First, most women with node-negative breast cancer will not relapse after local therapy. Second, the relative risk for recurrence can be predicted, though imperfectly, by current prognostic markers. Third, in appropriate patients, adjuvant chemotherapy or endocrine therapy can extend disease-free and, possibly, overall survival.

The physician must discuss estimates of prognosis and potential treatment benefits with the individual patient, and should consider other factors such as the general health and the presence of other disease. ER-negative tumors or large ER-positive tumors might be considered for adjuvant combination chemotherapy. Patients with ER-positive tumors, especially if they are relatively small, might be considered for adjuvant tamoxifen. Perhaps the most difficult decision is with the subset of patients with small, ER-positive, diploid tumors with a low S-phase fraction who have the lowest risk for recurrence (<10% at 5 years). A strong argument can be made for withholding adjuvant treatment in this subset.

TABLE I

Results of Early Ramdomized Trials Comparing Chemotherapy with "No Treatment" Control Arm

Study	Drugs	No. of Patients	Disease-Free Survival	Overall Survival
Nissen-Meyer	C	668	*	*
Ellis-Fischel	Ts	62	No Data	+
OSAKA	LMF	122	+	+
USSR III	Ts, TsMF	378	No Data	+
W. Midlands	LMF	467	0	No Data
Osaka	C±Mmc	229	+	No Data

* = Statistically significant benefit for treatment
+ = Trend in favor of treatment
0 = No benefit for treatment
C = cyclophosphamide; Ts = thiotepa; L = chlorambucil;
M = methotrexate; F = 5-fluorouracil; Mmc = mitromycin C

TABLE II

Three-Year Results of Milan Node-Negative Trial

Subset	Disease-Free Survival		Survival	
	Control	CMF	Control	CMF
All	50%	94%	82%	100%
Premenopausal	50%	87%	–	–
Postmenopausal	48%	100%	–	–

CMF = cyclophosphamide, methotrexate, 5-fluorouracil

TABLE III

Results of Recent Trials in Node-Negative Patients

Study	Drugs	Median Follow-up Time	Disease-Free Survival Control	Disease-Free Survival Treated
NSAPB (ER+)	Tam	4 yrs	77%	82%
NSABP (ER-)	MF	4 yrs	71%	80%
Intergroup[a]	CMFP	3 yrs	67%	84%

a = ER- or ER+ and >3 cm diameter
Tam = tamoxifen; MF = methotrexate and 5-fluorouracil;
CMFP = cyclophosphamide, methotrexate, 5-fluorouracil and prednisone

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LOCO-REGIONAL TREATMENT OF BREAST CANCER*

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The conservative treatment of early-stage breast carcinoma, often called "primary radiation therapy", is a combination of resection of the primary tumor with a surrounding margin of grossly normal breast tissue ("lumpectomy", "segmental mastectomy", or "quadrantectomy"), with or without surgical staging of the axilla, and radiation for the eradication of residual microscopic disease. The goal of such treatment is to provide highly satisfactory cosmetic results without compromising local tumor control or patient survival. This alternative to mastectomy has become increasingly popular since the results of randomized prospective studies have confirmed retrospective studies, which showed equal survival after conservative therapy and radical surgery.

This paper reviews some of these studies, describes the criteria of selection for such treatment and the correlates of tumor recurrence in the treated breast, and discusses the integration of adjuvant chemotherapy and radiation.

Retrospective Studies

Since the mid-1950s, many centres in Europe and North America have conducted trials of primary radiation therapy and much is known about the results of treatment (predominantly or exclusively) with supervoltage equipment. It is difficult to compare these series for many reasons, including differences in patient selection, surgical techniques, treatment machines, delivered dose and dose distributions, surgical and clinical staging of patients, different methods of data presentations and analysis, and changes in treatment policies and techniques with time.

These retrospective analyses permit conclusions concerning the time course to local recurrence and the ability to cure patients with mastectomy following failure of initial treatment. Although many will have local-regional recurrences after mastectomy within the first several years, patients treated with primary radiation therapy must be observed for local recurrence for a much longer time. These points are illustrated by a collaborative retrospective review of 152 patients irradiated before 1967 at the Institut Curie, the Marseilles Cancer Institute, or the Princess Margaret Hospital, Toronto. Minimum follow-up was 15 years. The techniques and doses used during this period were less satisfactory than current ones.

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Although most breast recurrences occurred during the first five years, the actuarial risk of local recurrence was nearly constant for 14 years after treatment. No local recurrences were seen between 15 and 20 years. The salvage of patients who developed a local-regional recurrence with subsequent surgery (usually mastectomy) yielded 58% freedom from distant metastases at 5 years, and 50% at 10 years. This salvage is much higher than for patients having a loco-regional recurrence following mastectomy. Thus, patients treated with conservative surgery and radiation need to be followed with careful physical examination and annual mammograms indefinitely, to detect both potentially curable local recurrence and new contralateral breast tumors.

Prospective Studies

Since 1970, prospective randomized trials using better radiation techniques have appeared, one in Italy, one in France, one in England, and two in the United States (one of these included Canada). The largest North American trial -- the National Surgical Adjuvant Breast Project (NSABP) B-06 study -- began a three-arm trial in 1976 comparing mastectomy to segmental mastectomy, with or without radiation.

The trial entered 1843 evaluable patients with clinical Stage I or II carcinoma with the primary clinically measuring up to 4 cm in size. Segmental mastectomy consisted of resection of the tumor with only enough normal tissue around it to ensure that the specimen margins were tumor-free. It was considered impossible to obtain tumor-free margins in 10% of the patients randomly assigned to segmental mastectomy, and total mastectomy was carried out in these patients. Radiation was delivered to the breast alone to a dose of 5000 to 5300 cGy in five to six weeks. The regional lymph nodes were not treated, and no boost was given to the tumor site.

The 5-year actuarial incidence of recurrence in the breast was 7% in the patients who received radiation, compared with 32% in patients who did not have radiation. This marked difference was seen both in patients with histologically involved and uninvolved lymph nodes. Patients with involved lymph nodes treated with segmental mastectomy and adjuvant chemotherapy (but without radiation) had a greater risk of breast recurrence (38%) than did patients with uninvolved nodes treated only with segmental mastectomy (28%). However, patients with involved nodes, who received radiation as well chemotherapy, had a smaller risk of breast cancer recurrence (4%) than did patients with uninvolved nodes treated with segmental mastectomy and radiation (9%). This suggests that chemotherapy by itself does little to prevent breast recurrence, but that radiation and chemotherapy may be additive or synergistic in reducing tumor recurrence in the breast.

A trend was also seen in node-negative patients; the incidence of distant metastases was higher in those patients treated with excision alone, compared with those who had excision plus radiotherapy. If confirmed by further follow-up, this trend suggests that the effectiveness of local control techniques may have an impact on patient survival, particularly for patients whose cancer is of an early stage. Patients with uninvolved nodes probably have the greatest potential for cure by effective local-regional treatment alone. Patients with involved nodes appear much more likely to have systemic subclinical disease at initial presentation, and of local treatment may have less of an impact on their survival.

These data support a position midway between the classical Halstedian view of breast carcinoma as a predominantly local-regional disease and the idea that breast cancer is almost inevitably a systemic disease. Whether there is a subset of patients (with tumors with particular pathologic and clinical features) that can be treated safely with conservative surgery alone is as yet unclear. To clarify these questions, I believe that wide local excision alone should be used only as part of a well-defined protocol, such as in a study that recently was closed in Ontario.

Cosmetic Results of Conservative Surgery and Radiotherapy

The cosmetic results after treatment with conservative surgery and radiation generally have been good to excellent, with nearly all patients being satisfied with their results. The results were found to depend on the dose and technique of radiation as well as the extent of surgery.

Patient Selection Criteria

The major criteria for patient selection for primary radiation therapy are: 1) the ability to resect the primary without causing major cosmetic deformities; and 2) the likelihood of breast recurrence.

Poor candidates for breast-conserving treatment are patients with two non-adjacent primaries in the same breast (demonstrated either by palpation or mammographically) and those in whom mammograms reveal extensive microcalcifications. One would expect the rate of breast recurrence in these patients to be substantially higher because the radiation dose tolerated by the entire breast is less likely to control the greater numbers of residual tumor cells.

Modern film-screen mammography often provides critical information in the initial evaluation of patients and should be done routinely before accepting patients for this treatment. Mammography should be performed before biopsy, if possible, in order to avoid obscuring potentially important details by postoperative scarring or hematoma.

The location of the tumor is an important consideration in patients with subareaolar primaries. For such patients to be treated successfully with primary radiation, resection of the nipple-areaola complex may be necessary.

With respect to the extent of surgical resection before radiation, wide margins do not appear necessary to achieve excellent local control rates provided the dose of radiation is adequate.

Patients who have microscopically involved ("positive") margins can be treated with a boost to the primary site to doses of at least 6000cGy. This achieves local tumor control in those with close or involved margins (with the possible exception of patients in certain pathologic subgroups). It is essential that the pathologist ink the margins of resection before cutting the specimen so that they can be identified clearly on microscopic examination.

Pathologic Correlates of Recurrence in the Treated Breast

Concerning the influence of the pathologic features of the excision specimen on the subsequent risk of local recurrences, the only feature shown to have a statistically significant impact on the local recurrence rate was the presence of an "extensive intraductal component" (EIC).

A tumor falls in this category only when two features are simultaneously present: 1) intraductal carcinoma comprising 25% or more of the area of the primary mass; and 2) intraductal carcinoma clearly extending beyond the infiltrating margin of the tumor or present in sections of grossly normal adjacent breast tissue. A tumor that has only focal invasion in a background of intraductal carcinoma also fits into this category.

We have no explanation for the association of EIC with a high risk of local recurrence, but it seems likely that these patients have a greater residual tumor burden following gross excision than do other patients. In a group of patients who underwent re-excision of the primary site, patients with an EIC in the initial specimen were more likely to have residual cancer than other patients.

In patients with an EIC, we review carefully the specimen and mammograms to be certain that the areas of intraductal spread have been excised adequately. The specimen should be examined closely to see whether there are any microcalcifications. If an EIC is present and the margins are involved microscopically or are equivocal, then a re-excision of the biopsy site should be done. If the margins of the re-excision specimen also are involved, then one might proceed to mastectomy.

Integration of Radiation and Adjuvant Chemotherapy

We have seen more acute reactions and worse long-term cosmetic results with concurrent chemotherapy and radiation than with sequential treatment. There is no difference in survival between these two approaches. To determine the optimal timing of chemotherapy and radiation, we have begun a prospective randomized trial for patients who will receive primary radiation. Patients with involved axillary nodes are randomized to receive four cycles, each lasting three weeks, consisting of cyclophosphamide, dexorubicin, methotrexate with leucovorin rescue, 5-fluorouracil, and prednisone, either before or following completion of radiation. So far, this regimen has been well-tolerated, with equal drug doses being tolerated by the patients in each arm. When patients are not treated on this protocol, we do not give more than three months of chemotherapy before beginning irradiation, to minimize the likelihood of tumor growth within the breast should chemotherapy prove ineffective.

Conclusion

When patients are properly selected for treatment and when it is competently performed, conservative surgery and radiation in those with early-stage, breast carcinomas give excellent cosmetic results and a high likelihood of preventing a recurrence. The chance of cure with this therapy is at least as good as with a mastectomy.

The major criteria of patient selection are: 1) the ability to resect the primary without causing major cosmetic deformities; and 2) the likelihood of breast recurrence. There is disagreement over the details.

Most breast recurrences occur during the first 5 years, but they can be seen as long as 14 years or more after treatment. Since surgical salvage of those who develop a local recurrence is high, patients treated with conservative surgery and radiation need to be followed indefinitely with careful physical examinations and annual mamograms. This is to detect both potentially curable local recurrences and new contralateral breast tumors.

At present, there is no consensus as to the optimal timing of chemotherapy and radiation.

When operation is performed competently and patients are selected properly for treatment, the use of a conservative procedure and radiation in patients with early-stage breast carcinomas will prevent a breast recurrence and give excellent cosmetic results. To obtain these results, it is essential to have co-operation between the surgeon, radiologist, pathologist, medical oncologist, and radiation therapist.

References available on request to author.

CARCINOMA OF THE CERVIX: EARLY DETECTION

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In 1980, Parkin et al[1] estimated that cancer of the cervix was the second most common cancer occurring world-wide. In Ontario and in the rest of Canada[2], it is less common: cancers of the breast, colorectum, lung, ovary, uterus and malignant melanoma are more frequent. In addition to cancer deaths from the aforementioned sites, deaths from pancreatic and stomach cancer occur more frequently than those from cancer of the cervix.

In Ontario, between 1964 and 1986, the age-adjusted incidence rate has declined steadily from 22.5 per 100,000 to 9.2 per 100,000. Mortality data for the province, which are available for a longer interval, show the same pattern, with a fall between 1950 and 1987 from 9.3 to 2.7 per 100,000.

In August 1941, the *American Journal of Obstetrics and Gynecology* published a paper by Papanicolou and Trant "The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus"[3]. This paper, the culmination of more than two decades of work, led to the use of the "Pap" smear in the early detection of preinvasive cancers of the cervix.

Because mortality rates began to fall before the widespread introduction of screening using cervical smears[4,5], many have asked whether the reduction in mortality and incidence might not be the result of improved socioeconomic status or hygiene and some have stated that there was no evidence that the use of the Pap smear was responsible for the decline in mortality.

In retrospect, it was perhaps unfortunate that randomized clinical trials were not undertaken before screening using the Pap smear came into widespread use in the late sixties. In the absence of such studies, it was difficult to evaluate the conflicting evidence obtained from initial comparisons between times or places, with and without programs of Pap smear screening. These comparisons were subject to many biases, which justified criticism of the early studies that found the procedure effective. As a result, in 1973, the Ontario Council of Health[6] recommended a case-control study in which all potential "confounding factors" could be identified and taken into account. The Ontario Cancer Treatment and Research Foundation funded such a study in Toronto, the first of its kind performed to evaluate a preventive measure in cancer. The initial results, published in 1979[7], demonstrated a three-fold protective effect for women who had had a Pap smear in the previous 5 years. It found that the lowest proportion of smears were reported in women over 60, in those with an household annual income of less than $10,000 and those who had not attended high school. Nevertheless the protective effect remained unchanged when standardized for age, income, education, marital status, age at marriage or age at first intercourse. Also the study found that, when the analysis was confined to those women who had visited a physician in the last 5 years, the proportion of cases, who had had a Pap smear, was significantly lower than in the controls; this difference was greater in the poor and the elderly. This observation suggests that not all physicians were aware of the importance of Pap screening these groups.

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Since the publication of the Toronto case-control study in 1979, case control studies of the Pap smear and cervical cancer elsewhere in the world have given similar results: all confirm the protective effect of the Pap smear[8-11].

In addition, during the seventies, further comparative studies related the fall in incidence and mortality to the intensity of screening. Miller el al[12] correlated the extent of screening with the fall in mortality in Canada at the provincial and the county or census district level. They demonstrated a significant effect of the intensity of screening on the fall in mortality, taking into account indices of income, education, housing and sanitation from 1961 and 1971.

In the Nordic contries, the evidence was more conclusive. In Norway, screening began in 1960 and was restricted to one county. In Denmark, screening began at the same time but covered only about 40% of the women in that country. Finland, Iceland and Sweden all have nationwide programs, which began in 1970, 1969 and 1973 respectively. Hakama[13] demonstrated a reduction in the incidence of the disease following the introduction of an organized program. This reduction occurred at the appropriate time period after the introduction of screening and the effect was restricted to those age groups to whom screening had been offered. Recently, Laara et al[14] demonstrated that, between 1965 and 1982, the fall in mortality from cervical cancer was greatest in Iceland (80%) and lowest in Norway (10%).

In 1976, based on the results of comparative studies, a task force on cervical screening programs, chaired by Dr. J.R. Walton[15], recommended that women who were not at high risk and whose initial two smears were negative should be screened every 3 years to age 35, and then every 5 years to age 60. Additional recommendations pertained to quality control in cytology laboratories, follow-up mechanisms, including the establishment of provincial cytology registries and uniform terminology. In 1982, the reconvened Task Force modified the recommendations to state that sexually active women should be screened annually from 18 to 35 years of age and thereafter every 5 years. The 1982 recommendation almost doubled the number of women who would require screening each year in Ontario from 722,200 to 1,529,000.

In 1979, the International Agency for Research on Cancer (IARC) formed a working group comprising representatives from jurisdictions which had organized screening programs, from investigators undertaking case-control studies and other experts. The objective was to amalgamate data from 10 centres, including Toronto, to determine sojourn time (the length of time that lesions remain detectable before surfacing clinically) and sensitivity. The conclusions were as follows:

- In the first 2 years after at least two negative cervical smears, the risk of invasive cancer was found to be less than 10% of that among unscreened women.
- From 3 to 10 years, after at least two negative smears, the risk of invasive cancer slowly increased. Compared to unscreened women, the cumulative rate was approximately 9% in the first 3 years, 15% in the first 5 years and 42% in the first 10 years.
- The false-negative rates varied widely from values approaching 40% to values of less than 10%. The lowest false-negative rates were seen from centrally organized programs such as Iceland, Sweden and Aberdeen[16].

Day[17], using these data, assessed the effect of different screening frequencies, starting at age 20, in terms of the cumulative incidence rate for cervical cancer, assuming rates similar to those in Western Europe, which are similar to those in Ontario. The cumulative incidence rate is a measure of the risk an individual would have of developing cervical cancer betwen age 20-64 if death from another cause did not occur[18]. Some of the results of different screening intervals are shown in Table I. It is evident that screening every year from ages 20 to 34, and then every 5 years, as opposed to screening every 5 years, reduces the cumulative incidence rate by an additional 2%.

TABLE I

Effect of Different Screening Policies (starting at age 20)

Screening Schedule		% Reduction in Cumulative Rate	Number of Tests
Screening every 5 years	20-64	83.6	9
Screening every 5 years	35-64	81.0	6
Screening every year then every 5 years	20-34	85.5	21

In its final report, the IARC working group recommended that screening programs should be aimed principally at women aged 35-60 but should start some years before age 35 and that the intervals between screening should be 3 years or less[16]. They emphasized that the aim of screening is to prevent invasive cancer, not simply to detect preinvasive lesions.

The IARC recommendations would require the screening of 100,000 more women each year in Ontario than the 1976 Canadian recommendations. However, because we have no organized cervical screening program in Ontario, we do not know whether the 1976 or 1982 Canadian recommendations are being followed or possibly those of the 1986 IARC working group. In 1973 the Ontario Health Insurance Plan paid more than 6 million dollars for the reading of 696,000 smears. Ten years later, in 1982, almost one million smears were read at a cost of more than 9 million dollars and yet, in these 10 years, the cumulative incidence rate of invasive cervical cancer dropped by a mere 29%, from 1.11 to 0.79, as opposed to the 80% or more postulated by Day.

It is evident that, in the absence of an organized program, the Province of Ontario is spending a considerable number of health dollars on ad hoc screening for cancer of the cervix but is not achieving the desired benefit. In addition, there is no means to determine whether women in some age groups are being screened more frequently than recommended or whether women in older age groups are being adequately screened. Based on an Access to Health Care Survey in the USA in 1986, the frequency of Pap smears was low in older women, those that were below the poverty level and those who had not graduated from high school. This finding is similar to that reported in Toronto 10 years earlier. These observations suggest that our aim should be to ensure that all women, who have been sexually active, be screened at regular intervals.

In the Toronto study the results of the smears in 19 of the 31 women (who developed invasive cancer between 1973 and 1976 and had been screened) were abnormal for 1 to 6 years before diagnosis[19]. A provincial cytology registry might have ensured more prompt treatment of these women and thus prevented progression to invasive cancer.

In conclusion, we have unequivocal evidence, based on criteria established by the Task Force on the Periodic Health Examination[20], even in the absence of a randomized clinical trial, that screening for cervical cancer using the Pap smear is effective. In view of the years that have elapsed since the last Canadian recommendations, and the evidence accumulated in the interim, particularly by the IARC working group, it is time to re-examine our recommendations for cervical screening in Canada. A workshop is required such as that held recently under the aegis of the Deputy Ministers of Health to develop recommendations for screening carcinoma of the breast[21]. The principal objective of this workshop would be to develop new Canadian recommendations for cervical screening.

An organized program of cervical screening in Ontario would provide:

- individual identification of women;

- measures to ensure that all women at risk are screened;
- adequate facilities for treating abnormalities;
- a "failsafe" mechanism to ensure that a woman with a definitive abnormality is treated appropriately and is not lost to the health-care system;
- a system of quality control;
- monitoring and evaluation of the program.

In spite of the controversy surrounding treatment of early grades of cervical intraepithelial neoplasia, and ignoring the question of insufficient colposcopy facilities and the identification of human papillomavirus, it is evident that the incidence and mortality from cervical cancer has been reduced in several countries by taking smears adequately at regular intervals and treating significant abnormalities. In Ontario, steps should be taken to implement an organized program for screening for cervical cancer. This program could include the research needed to determine the significance of early cervical intraepithelial neoplasia and the contribution of the human papillomavirus to cervical cancer.

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EARLY DIAGNOSIS OF OVARIAN CARCINOMA*

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Ovarian carcinoma, the third most-common female malignancy in Sweden, accounts for almost 50% of gynecological cancer deaths. Studies of the stage distribution show that, at the moment of diagnosis, 76% of the women with ovarian cancer have disease outside the gynecological organs. According to our annual report, which collects data from all over the world, the 5-year total survival rate for ovarian cancer for the period 1979-1981 was 34.9%. Unfortunately, despite more aggressive treatment of ovarian carcinoma during the last few decades, the 5-year survival rate has not improved significantly. In Scandinavia, the mean age for diagnosis is around 65. Since the female population is getting older here we can expect a steady increase in the incidence of ovarian cancer during the next few decades. The projections of the Finnish Cancer Institute show that the incidence of ovarian carcinoma will increase steadily until year 2000.

The early diagnosis of ovarian cancer is difficult because of the lack of characteristic symptoms, difficulties in differential diagnosis and lack of screening methods. In the Stockholm area, Dr. Flam and coworkers have found that that the main reasons for seeking consultation and the main initial symptoms in patients with ovarian cancer were abdominal swelling, abdominal pain, and other gastrointestinal symptoms. They found no significant difference in symptomatology between the early and the more advanced cases. In this area the first consultant in most cases was a gynecologist and the doctor's delay in reaching a diagnosis was not remarkably long. However, these studies represent an urban experience and probably the delay is longer in a rural area. Probably in some cases, we can avoid the iatrogenic delay by educating our young physicians to refer women with pain or abdominal swelling for a gynecological examination. In addition, however, we have an urgent need for a reliable screening method for ovarian cancer.

In early diagnosis, ultrasound alone has not proved sensitive and specific enough as a screening method. The development of the monoclonal technology has opened new applications for biological markers. CA 125 is an antigen associated with most ovarian carcinoma. Many studies have been done to test the usefulness of CA 125 antibodies in early diagnosis. One of the first of these was done in Stockholm: the aim of this study was to determine if CA 125 would help to discriminate between malignant and benign disease of the ovary. From women undergoing laparatomy for pelvic masses, 219 sera were collected, immediately frozen and later investigated with analyses of their medical records. Another objective of the study was to identify those benign conditions that give rise to elevated CA 125 values and to determine if a panel of assays might enhance the specificity of CA 125 in differential diagnosis. Among those contributing the 219 sera were 165 patients with benign disease, and 26 of them had elevated CA 125 values. This series contained 27 patients with non-mucinous invasive ovarian carcinoma, of whom 26 had elevated CA 125 values. This represents 95% sensitivity and 85% specificity in differentiating between a pelvic mass and ovarian cancer. To enhance its specificity, two other assays -- TAG 72-3 and CA 15-3 -- have been added to CA 125. The addition of these two assays raises the specificity to 98% but decreases the sensitivity to 85%. Among the patients with false positive values, we found benign neoplasm, endometriosis, fibroids and pelvic inflammatory disease.

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Can CA 125 be used to screen for ovarian cancer in a healthy population? The Scandinavian countries and especially Sweden is a feasible place in which to undertake a pilot investigation concerning screening. Registration of patients provides total coverage of all malignancies and other diagnoses. A joint American-Swedish project started with a Phase I pilot investigation, which included 1082 women above 40 years of age. Phase I sought to identify and solve logistical and data management problems and to establish the feasibility of a larger prospective study. The protocol was based on non-invasive procedure. Blood samples were collected in Stockholm, frozen and transported for laboratory work-up in USA. Then women with elevated values and negative, matched controls had gynecological exams and ultrasound investigations twice a year and blood samples four times a year. The Swedish Tumor and In-Patient Registries did the follow-up.

We expected to find elevated values in 3.8% of the specimens. The observed value was 3.2%. Of these, 5.4% were premenopausal and 0.6% were postmenopausal. Among the population observed by the Tumor Registry, 10 women had non-invasive malignant disease at the time of observation. None of these had elevated CA 125 values. The only patient with elevated values and malignant disease had ovarian carcinoma.

We are gaining experience in screening for cervical and mammary carcinoma and know that every screening program we design will have both benefits and disadvantages. With respect ovarian cancer, the main objective of screening would be to detect the disease in its early stages and thus to decrease the mortality rate. If we could double the number of Stage I and II cases detected, the 5-year survival rate would increase from about 30% to about 55%.

We need to answer certain questions before we can establish the usefulness of

CA 125 as a screening procedure. Is the test sensitive enough? Is it specific enough? If the test is used as a screening procedure, will it reduce mortality? Also does the natural history of ovarian cancer make it suitable for screening? Until we answer these major questions, the CA 125 test should not be used as a screening procedure. Today we cannot say that the CA 125 assay is sensitive enough for a screening procedure. It must be studied in a much larger population, around 100,000 women. The Scandinavian countries with their 100% follow-up through Cancer Registry and In-Patient Registry is a suitable area for that kind of study.

In postmenopausal women, the CA 125 seems to be specific enough to justify further investigation, which would require mortality studies in a population of 100,000 women. Until that study has been done, we cannot establish the usefulness of CA 125 in early diagnosis.

Our studies of the early diagnosis of carcinoma of the cervix have demonstrated that poorly designed, unorganized screening will have great difficulty in proving a decrease in mortality in the population screened. For this reason, we believe that it is essential that a larger, well-designed study be carried out before we can say that screening of a healthy population with CA 125 will give meaningful results.

CARCINOMA OF THE OVARY – EARLY DISEASE: SURGICAL THERAPY*

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This paper will discuss epithalial (Mullerian) tumors of the ovary in those patients who, at the completion of their initial surgery, are left without gross disease within the peritoneal cavity. This means mostly Stage I disease although occasionally, by good fortune, at the completion of the primary procedure a patient with Stage II or III disease will fall into this category.

If there is a role for radiation in the primary treatment of these tumors, it is in this small group of patients who have microscopic evidence of spread beyond the ovary at the conclusion of primary surgery. Although there are now powerful cytotoxic agents, which can suppress or delay the progress of epithelial ovarian carcinoma, the introduction of these agents has not significantly changed the five-year survival in this cancer -- all stages.

In practical terms, in 1988, early diagnosis of carcinoma of the ovary is still a matter of pure chance. Routine well-woman examination, pelvic ultrasound screening, tumor-marker screening, all have been found wanting.

Therefore the most critical factor in the management of early ovarian disease is correct and complete surgical assessment at the time of the initial diagnosis. If the surgeon does his job properly, sound decisions regarding adjuvant therapy can be made and a reasonably accurate prognosis given to the patient and family. If the surgery is done improperly or is inadequate, the patient may be denied appropriate adjunctive therapy or, equally disappointing, she may receive such therapy with its potential long and short-terms toxicity when it is not needed.

The diagnosis of low-malignant-potential (LMP) ovarian carcinoma ("early disease") is becoming more common. From a surgical viewpoint, there is no difference between LMP ovarian and true ovarian cancer.

Before the surgeon takes a woman in the childbearing age to the operating theatre with suspected ovarian pathology, he must review with the patient, her future reproductive intentions because this may have an important bearing on what will be done at the time of surgery.

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Here are some general rules in the surgical management of early carcinoma of the ovary:

1. Do not aspirate cystic fluid for a preoperative diagnosis or during the operation to facilitate removal of the mass. In ovarian carcinoma, 80% of the cystic fluid is cytologically positive for malignant cells. Puncturing the cyst and spilling such fluid into the free peritoneal cavity may convert a Stage Ia carcinoma, which does not need further treatment, to a Stage Ic, which may require either adjunctive chemotherapy or radiation.

2. Always employ a vertical incision whenever there is any possibility of ovarian pathology. As Dr. Hugh Barber of New York has said: "To try to properly assess the peritoneal cavity through a Pfannenstiel's incision is like trying to scratch your armpit through your fly"!

3. At the beginning of the procedure through a small peritoneal incision, take a sample of ascites for cytological examination. If there is no ascites, with an Asepto syringe, put 200 or 300 cc of saline into the pelvic cavity, mix it with the peritoneal contents, remove this by suction and send it to the cytological laboratory.

4. Remove the cystic lesion intact -- extending the incision as needed. The decision regarding appropriate surgical management can be made by the surgeon on gross examination of the ovarian tumor. This should be done out of the operative field. When completed, the surgeon should change his gloves and gown before entering the operative field again. Quick section rarely has a role in the surgical management of early-stage ovarian cancer. If, on inspection, the ovarian mass is unilocular, if both external and internal surfaces are smooth, and if the tumor is fixed to adjacent tissue only by pressure adhesions, which are readily broken down, and there is no evidence of extension into the adjacent structres, then nothing further needs to be done. The ovarian pedicle should be reperitonealized and the abdomen closed. The tumor is almost certainly benign.

If the ovarian mass shows excrescences on the external or internal surfaces, if it shows areas of hemorrhage, edematous or gelatinous thickening of the cyst walls, if the mass is multilocular or fixed, and the patient has completed her family or is prepared to give up her reproductive capacity -- a total abdominal hysterectomy and bileteral salpingo-oophorectomy should be performed. An omentectomy should be performed at least to the antimesentery border of the transverse colon. Multiple peritoneal biopsies should be taken in both para-aortic gutters, from the pelvic floor, mesentery and both domes of diaphragm. Para-aortic and pelvic lymph nodes should be palpated and suspicious lymph nodes removed for pathological inspection. The cyst fluid should be sent separately for cytology. Finally, if there is any question that cystic fluid has been spilled during the procedure, the surgeon should take preclosure washings (as described).

If the patient is not prepared to give up her reproductice capacity in this situation, the other ovary should be inspected carefully and any suspicious excrescences or nodules biopsied. As well, as described above, omentectomy, multiple peritoneal biopsies, suspicious nodes, cystic fluid and preclosure washings should all be performed.

Only such careful and meticulous assessment of early ovarian cancer allows a proper decision concerning what, if any, adjunctive therapy is required.

Finally, I have been asked to report on the two National Cancer Institute of Canada ovarian trials (early disease), which were closed in January 1988, because of lack of adequate accrual.

NCIC OV.6 was a registration and follow-up study of those patients who had had a total abdominal hysterectory and bilateral salpingo-oophorectomy, *plus* complete assessment, as above described, and where there was no gross or microscopic evidence of spread of disease beyong the ovary. To date, 75 women have been followed with a median duration of 757 days. There have been two recurrences, one a serious lesion at 11 months, and one a clear-cell tumor at 21 months. Three patients had excrescences and 72 did not. The two recurrences were not in the excrescence group. As might have been anticipated, histologically, endometroid carcinomas were the most common, although there was a surprisingly large number of clear-cell carcinomas. Most of the tumors were of low grade.

The NCIC OV.7 trial attempted to answer the most critical contemporary question in the management of ovarian carcinoma. What is best -- total abdominal irradiation or chemotherapy, as adjuntive therapy in early ovarian disease (microscopic spread only). This was a simple randomization to optimal chemotherapy or optimal irradiation when, at the completion of surgery, there was only microscopic evidence of disseminated disease. This review suggests that radiation is the least toxic, at least during treatment. Although there have been recurrences in this small series (30), it is too early to compare arms. Even when the study matures, the differences may be too small for a series of this size to demonstrate.

OVARIAN CANCER: RADIOTHERAPY[*]

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Broadly speaking, postoperative patients with epithelial ovarian cancer present in two groups. The first, "good prognosis", are those in whom the disease has not spread beyond the peritoneal cavity or retroperitoneum, i.e. Stages I, II and III, and in whom one finds no macroscopic residual tumor or it is present only in small amounts. About 60% of these patients are alive five years after diagnosis and many are cured. It is in this group of patients that there is an indication for primary postoperative radiotherapy. In contrast, poor prognosis patients are those with disease that has spread to the liver or beyond the abdomen, i.e. Stage IV, or those who have large amounts of macroscopic tumor remaining in Stages II and III. Of these patients, only 5 to 10% are likely to achieve a long-term, disease-free status. In these patients, one should not give radiation with curative intent as the sole postoperative treatment but it might have a place in a combined strategy.

With the poor prognosis group, the negative prognostic effect of the large tumor residuum is so powerful that other prognostic factors, such as stage and tumor differentiation, influence outcome only to a minor degree. However, in the good prognosis group, prognosis and therefore treatment selection, are determined largely by cellular differentiation, presence or absence of tumor residuum, and FIGO (International Federation of Gynecology and Obstetrics) stage.

Primary Postoperative Abdominopelvic Radiation

As staging studies have demonstrated, transperitoneal spread is the most common route of dissemination of ovarian cancer. Furthermore, at the time of first relapse, tumor is confined to the abdominal cavity in about 85% of patients. Thus, it might be reasonable to expect that techniques of radiation, which encompass the whole peritoneal cavity, would be more likely to cure than those which treat the pelvis alone or just the lower abdomen. However, the dose of radiation that can be given to the upper abdomen is appreciably lower than that considered to be a radical dose for solid tumors. Therefore one would predict that whole abdominal irradiation would produce a modest improvement in tumor control in the upper abdomen and that the benefit would be seen only in those with microscopic volumes of tumor.

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To date none of the studies of Stage I ovarian cancer have demonstrated that postoperative therapy confers a survival benefit. This applies to studies of chemotherapy, intraperitoneal isotopes, and external-beam radiation. Investigators attempting to establish a role for postoperative therapy in Stage I face two kinds of problems. On the one hand, Stage I is an uncommon presentation when the patient has had thorough intraoperative staging exploration. With the baseline survival rate in Stage I of 70 to 80%, one probably cannot show statistical improvement in outcome without a large patient sample size. On the other hand, physicians are reluctant to recommend toxic therapies in Stage I, where the majority of patients are cured by operation alone and where simple treatment methods have failed to show a benefit. Our approach in Toronto has been to identify those Stage I patients with a high risk of relapse, namely those with moderately and poorly differentiated tumors, or well-differentiated tumors with positive peritoneal cytology, and those with densely adherent tumors, and direct postoperative treatment onto to this sub-group. It is recommended that "unfavorable" Stage I patients receive pelvic plus abdominopelvic radiation because it has been shown to be superior to pelvic radiation in those with more advanced disease. To date it has not been proved more effective than surgery alone. Patients with Stage I disease that is well differentiated, and in whom, at operation, the tumor was not densely adherent to adjacent structures have a high cure rate by operation alone (over 95%) and in them postoperative treatment is not indicated.

One randomized study and a few non-randomized studies have indicated a superior outcome for patients treated with abdominopelvic compared with pelvic radiation. In Stages IB, II, and III, the Princess Margaret Hospital study showed a statistically significant benefit for the patients treated with abdominopelvic radiation. This benefit, which was confined to those who had small or no macroscopic residual disease, consisted of a 25% reduction in the risk of upper abdominal tumor relapse and a 25% improvement in long-term survival[1]. Thus, when radiation is the primary postoperative treatment, it should encompass the whole abdominal cavity and the liver should not be shielded.

Whole abdominal radiation has been administered by treating small segments of the abdomen in a sequential fashion ("the moving strip technique") or by treating the entire peritoneal contents each day ("the open beam technique"). These two techniques have been compared in two randomized studies[2,3]; in both, the difference in 5-year survival between the two treatment arms was less than 1%. In addition, the open-beam technique, which uses smaller daily doses, was associated with a lower risk of late bowel complications. Nowadays, the open-beam technique is preferred because it is shorter in overall duration and technically simpler.

The evidence that radiation may cure patients with epithelial ovarian cancer is derived from examining long-term survival data in those who had known residual tumor after operation. Because fewer than 1% of relapses occur beyond 8 years from diagnosis, 10-year, relapse-free rates and survival rates provide good measures of cure. The most rigorous estimate of the curative value of postoperative treatment in ovarian cancer is obtained by examining the outcome only in those patients with known macroscopic residual tumor after primary operation. This is because an appreciable proportion of patients who have all macroscopic tumor resected are cured by the procedure itself. Table I summarizes 10-year results for Stages II, and III from three reports[4-6]. These results, which are similar for all three series, provide strong evidence for the curative potential of this treatment. They show that about 40 to 50% of patients with lesions smaller than 2 cm achieve long-term disease-free status. Few patients with lesions larger than 2 cm are cured by radiation (or chemotherapy). In patients with large residual tumors, chemotherapy provides longer relapse-free intervals and so is preferred as the initial treatment.

As has been implied, patients for whom abdominopelvic radiation constitutes definitive postoperative treatment are derived from those who have Stage I grades II and III, and Stages II, and III with completely resected disease or with small residual tumor confined to the true pelvis. In this group, the prognostic variables: stage, presence or absence of residuum, and histopathology, all independently influence outcome. The information from these three variables can be combined to subdivide the good prognosis group into two subgroups (Fig. 1)[4]. Fig. 2 shows treatment results. Approximately 70% of those treated with abdominopelvic radiation remain disease-free in the intermediate risk (unshaded), compared with 20% in the high risk subgroup (shaded). Intermediate risk makes up approximately one-third of all postoperative cases; these are the patients for whom abdominopelvic radiation is definitive postoperative treatment. If grades I, II, and III are substituted for the three-tiered histopathology shown in Fig. 1, a similar subdivision of patients is created[4]. Patients in the high-risk group should be treated with chemotherapy or combined chemoradiotherapy.

Since most papers on radiotherapy emphasize early-stage ovarian cancer and most reports on chemotherapy emphasize advanced stages, there is some debate whether patients with small-volume, residual disease in Stages I, II, and III (intermediate risk and high risk) are better treated by abdominopelvic radiation or platinum-based combination chemotherapy. In published reports, the complexity of the disease and the different patient-selection factors makes it impossible to be certain whether the two treatments are equivalent in these patients, or whether one might show superiority with respect to cure. To answer this important question, we must await a direct comparison in a randomized trial. Unfortunately the two treatments are so different that it is difficult to present the options to patients for informed consent. Moreover, most physicians have a strong bias toward one treatment or the other. For these reasons several co-operative studies, which attempted to compare abdominopelvic radiation and platinum-based combination chemotherapy have been forced to close because of poor patient accrual.

Side effects of abdominopelvic radiation included generalized fatigue, nausea, and mild diarrhea. Neutropenia and thrombocytopenia also can occur. The most frequent cause of serious late toxicity is bowel damage. The risk of such damage can be related to increasing total radiation dose, increasing dose per fraction, the extent

TABLE I
Long-term Outcome Following Abdominopelvic Radiation by Stage and Macroscopic Residuum

Centre		Residuum Size					
		None		<2 cm		>2 cm	
Princess Margaret Hospital[(4)]	Stage	II	III	II	III	II	III
	Number	108	46	36	55	36	71
	%S_5	74	48	58	43	39	18
	%RFR_{10}	65	40	54	28	0	7
Stanford/Mayo Clinic[(5)]	Number	30		40		54	
	%RFR_{10}	62		50		14	
Walter Reed Hospital[(6)]	Number	24		24		20	
	%S_{10}	59		42		10	

S = survival rate; RFR = relapse-free rate
In each case, the subscript number refers to the year after diagnosis

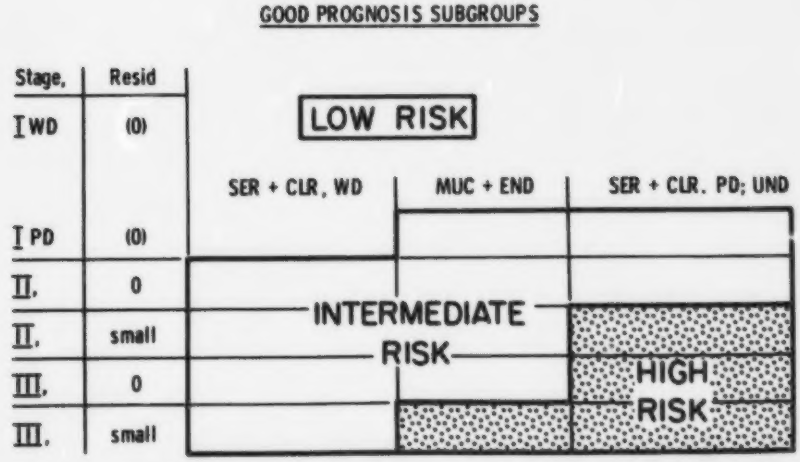
GOOD PROGNOSIS SUBGROUPS
Stage,
Resid
I WD
(0)
I PD
(0)
II.
0
II.
small
III.
0
III.
small
LOW RISK
SER + CLR, WD
MUC + END
SER + CLR. PD; UND
INTERMEDIATE RISK
HIGH RISK

Fig. 1 **The classification of patients with epithelial ovarian cancer, Stages I, II and III, having small nor no macroscopic residuum. Risk factors are defined according to the prognostic factors stage, residuum and histopathology.**
(Resid = residuum; PD = grades 2 and 3; WD = grade 1; SER = serous; MUC = mucinous; END = endometrioid; CLR = clear cell; UND = unclassified or undifferentiated)

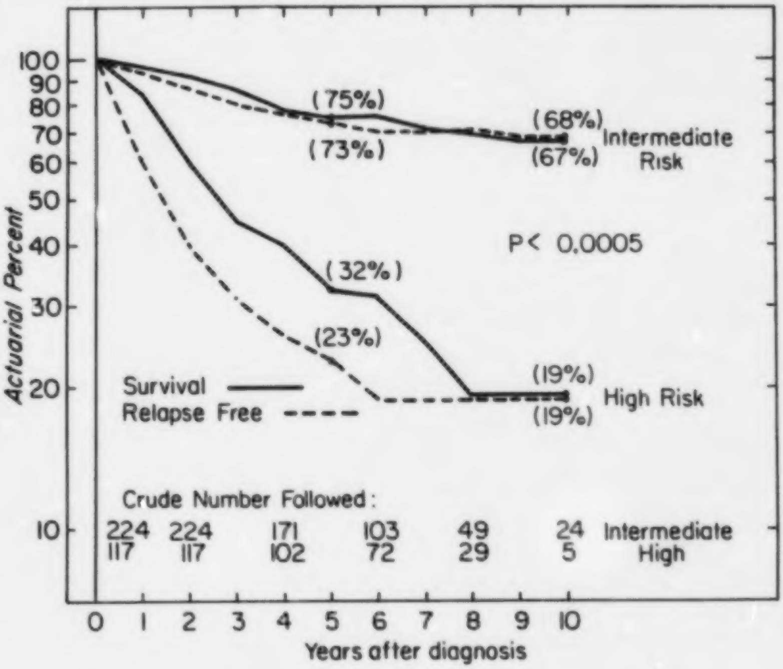

Fig. 2 Survival curves (including all causes of death) and relapse-free curves of 341 patients classified as intermediate- or high-risk in Fig. 1. The percentages in parentheses are the 5- and 10-year rates.

and number of previous abdominal operations, and possibly previous combination chemotherapy. If one employs daily doses in the order of 100 to 125 cGy, and keeps the total dose to the abdominal below 2750 cGy, and the dose to the pelvis below 4500 cGy, the risk of serious bowel toxicity is less than 5%[4].

Sequential Chemotherapy-Radiation

Following the demonstration that patients with early presentations and small amounts of residual tumor can be cured with abdominopelvic radiation, many centres have begun to treat patients, who have minimal disease after chemotherapy, with radiotherapy. The theoretical rationale remains to be validated by clinical experience, and most published reports are null or inconclusive. The expected benefit is small because, after chemotherapy, most patients with uncured disease (no matter how small the remaining volume) would still meet high risk criteria at best. Moreover, because of myelotoxicity during chemotherapy, 20% of patients cannot tolerate a therapeutic dose of radiation. In the context of sequential multiple-modality therapy, two important causes of radiation resistance should be considered . The first is the effect of tumor proliferation during a course of multiple modality treatment, which lasts several months. Mounting evidence suggests that cytoreductive stimuli such as radiation or chemotherapy may stimulate the proliferation of clonogenic cells within the tumor and may cause treatment failure. In an attempt to shorten overall treatment time and reduce the negative effect of proliferation, some investigators are studying twice-a-day radiation. The second possiblity is true cellular resistance. Studies using human-ovarian-cancer cell lines have shown that in vitro radiation sensitivity is less in the cell lines resistant to cisplatin and melphalan, than in the parent drug-sensitive cell lines[7]. In the clinical situation, it is possible that tumor cells, which persist after platinum-based chemotherapy, are less radiosensitive than those encountered in the primary postoperative situation. Patients most likely to benefit from abdominopelvic radiation after chemotherapy are those with the smallest volume of disease, i.e. microscopic positive or negative second-look laparotomy, those with well-differentiated tumors, and those who had good hematologic tolerance of chemotherapy. Proof of the benefit of sequential therapy will require a randomized study and, at present, the potential benefit of this approach is uncertain.

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CHEMOTHERAPY IN EARLY-STAGE OVARIAN CANCER*

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Because most studies that assessed the efficacy of chemotherapy in early-stage ovarian cancer used single alkylating agents, it is against this standard that other treatments have been compared. These earlier studies demonstrate a number of points:

1. Randomized studies comparing no treatment with pelvic radiation reveal no differences in recurrence rates. This conclusion is confirmed by calculating weighted averages between these groups.

2. While no studies have compared no treatment with pelvic radiation or whole-abdominal radiation, weighted averages for all studies combined reveal no differences between these various groups.

3. Studies comparing single alkylating chemotherapy with abdominopelvic radiation or intraperitoneal P-32 shows no advantage for either method. In 1979 and 1984 studies of Dembo *et al*, chemotherapy *plus* pelvic radiation was inferior to whole abdominal radiation. This study did not address the impact of radiation on the patient's ability to tolerate appropriate doses of the various drugs. These data are at variance with other studies comparing radiation with chemotherapy.

Furthermore, recurrence rates in the chemotherapy arm were the highest ever recorded in a study of early-stage ovarian cancer -- even higher than all non-treatment arms, implying that, in this study, the chemotherapy arm concealed a bias of high-risk factors.

Only in their 1980 study did Hreshchyshyn *et al* find that a single alkylating agent was more effective than no treatment or pelvic radiation. In this gynecology and obstetrics group study, more than 50% of patients were excluded for a variety of reasons, including "borderline" pathology (18%) and physician and patient preferences. This high rate of exclusion has been appropriately criticized. However, equal numbers of patients were excluded from each of the three arms of the study and the bias of good prognostic factors operated toward the no-treatment arm. It is not surprising, therefore, that responses to pelvic radiation were inferior to those of no treatment. Despite this, the study identified a statistically significant difference in Stage 1A poorly differentiated tumors for a single alkylating agent, compared to pelvic radiation or no treatment.

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It should be stressed that many ovarian carcinoma studies were flawed by inattention to significant risk factors. These include inadequate chemotherapy, inadequate attention to borderline pathology, and inadequate consistency in defining risk. The problems that derive from inadequate attention to staging, are especially pertinent to this discussion.

In 1983, Young *et al* reported that 31% of patients assumed to be Stage I were assigned to a higher stage after pathosurgical staging. Subsequently, in 1985, McGowen et al showed that over 50% of patients referred for treatment of ovarian carcinoma had been incompletely staged.

Only in two studies of Stage I ovarian carcinoma did the authors carry out pathological staging. The first, (Young et al 1983) found no differences between no treatment and single alkylating agent chemotherapy for favorable Stage I disease; both had more than 90% cure rate. In the second (Young *et al* 1987), patients with unfavorable Stage I disease had an 80% cure rate whether they received intraperitoneal P-32 or a single alkylating agent.

The Princess Margaret Hospital (PMH) data (Dembo 1982) demonstrate conclusively that stage has a significant impact on outcome. Patients with non-pathologically staged I and II disease without macroscopic residuum had a 74-76% five-year survival following whole-abdominal radiation. If we assume that 30% of Stage I and II patients likely would have been assigned a higher stage if they had been subjected to a staging laparotomy, under these circumstances, 48% would have survived five years. This adjustment to the PMH radiation data may allow us to predict that close to 90% of surgically Stage I patients might have survived after whole-abdominal radiation.

It should be noted that patients win the PMH studies with macroscopic residual Stage II and all those with Stage III disease did not do as well as in Stage I patients when treated with whole-abdominal radiation alone. Based on historical data already presented, the same outcome may be predicted with chemotherapy. However, it is important to recognize that, for many years, it was assumed that single alkylating agents were the treatment of choice for ovarian cancer. Indeed, some authorities still believe this to be the case.

In 1983, in an historic study, Young *et al* showed that multiagent chemotherapy was superior to a single alkylating agent in ovarian cancer. Although many criticized it for methodological reasons, this report stimulated a burst of clinical trials research in this area. Subsequently, the clinical trials of multiagent chemotherapy have shown many discrepancies, and have produced more questions than answers. While these discrepancies were due, in part, to inattention to risk factors, a dose-intensity analysis of 39 randomized studies of ovarian cancer chemotherapy by L. Levin and W.M. Hryniuk seemed to demonstrate a consistent pattern. These authors showed that, when dose intensity was calculated relative to a chosen standard, outcome was significantly influenced by average dose intensity. On futher analysis, there was no dose-intensity relationship to outcome for cyclophosphamide or Adriamycin, but there was a significant relationship between increasing dose intensity of cisplatin and both clinical response and survival. Here cisplatin made a disproportionate contribution to outcome after one combines all study arms. Weighted averages of these responses revealed a significantly improved survival for patients treated with cisplatin alone or with multiagent regimens containing cisplatin, when compared with single alkylating agents alone or multiagent chemotherapy not containing cisplatin. Clinical response showed a similar significant improvement for cisplatin-containing regimens. The dose-intensity effect of cisplatin accounted for 67% of the variation in responses encountered in various studies.

The dose-intensity analysis demonstrated that, almost certainly, outcome is influenced by the type of chemotherapy and, in particular, the incorporation of cisplatin in a dose-intensive way. Based on this analysis, we predict that patients treated with platinum-based multiagent chemotherapy will do better than those treated with a single-alkylating agent.

While no specific studies have addressed the impact of multiagent chemotherapy on minimal residual disease in ovarian cancer, a review of studies, which provide response to treatment and a breakdown of patients with Stage III and less than 2 cm of residual disease, permit the following conclusions: Three-year survival for Stage III that has less than 2 cm residual disease is remarkably consistent between these various studies and show a 67% weighted average. This outcome compares with a 45% five-year survival for whole abdominal radiation reported by A.J. Dembo in 1984 and by Weiser et al in 1988.

Clearly these comparisons are not accurate because they are based on three-year *versus* five-year survival rates. However one chemotherapy study reported a five-year survival of 65%. This issue can be resolved only by a prospective randomized study, which compares whole-abdominal radiation with dose-intensive, platinum-based chemotherapy. Recently, a National Cancer Institute of Canada study attempted to do this but failed to accrue a sufficient number of patients.

These are my recommendations for chemotherapy in early-stage ovarian cancer. It is indicated for those patients who have been pathologically staged and found to have a Stage II macroscopic residual greater than 2 cm, Stage III macroscopic residual disease and all those with Stage IV disease. Based on our information at this time, I consider that patients with Stage I high-risk disease and those with Stage II, microscopic residual disease are candidates for whole-abdominal radiation. I prefer to treat patients with Stage II macroscopic residual less than 2 cm and Stage III microscopic residual disease with cisplatin-based multiagent chemotherapy. I see no indication for chemotherapy in patients with Stage I low-risk disease.

For the present, treatment chosen for early-stage ovarian cancer will be dictated chiefly by local preferences, although, as this paper has shown, current experience provides some solid data to assist in these decisions.

References available on request to author.

THE IMPACT OF EARLY DETECTION AND STATE-OF-THE-ART TREATMENT ON CANCER CONTROL*

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To many persons cancer seems almost invincible -- it cannot be prevented and once detected no treatment is truly effective. This paper discusses the extent to which the cancer control effort -- specifically the early detection of cancer and modern cancer treatments -- can reduce cancer mortality. First it will discuss the various interventions in cancer control, namely, prevention, screening, early detection, and treatment. Then it will outline the methods and mathematical models, which might be used in the estimation of the impact of these interventions. Also we will note the manner in which we incorporate the degree of certainty or criteria of evidence into the estimation of impact. We also discuss the reasons why these analyses are important and how they can be used to establish public policy and cancer control agendas.

The National Cancer Institute (NCI) of the United States has performed these and similar analyses and has formulated program objectives, cancer control public policy and research directions, based in part, on these analyses. We also discuss briefly the recent progress of the United States in meeting its cancer control objectives.

Framework

Cancer Control: This term refers to steps taken to reduce the morbidity and mortality from cancer, namely, screening and early detection, treatment and rehabilitation. At the NCI, as part of cancer control, we include research to develop, validate, demonstrate, apply and evaluate cancer-control regimens.

In the early part of this decade, the Cancer Control Program of the NCI was reorganized into five research phases[1]. Phases I and II constitute the development of ideas related to cancer control, and the formulation of the specific hypotheses or regimens to be evaluated during subsequent research phases. Phase III refers to clinical trial research, namely, the precise validation of intervention regimens using classical techniques of evaluation. Often, however, the regimens do not lend themselves to evaluation by the clinical trials method and quasi-experimental evaluation designs are necessary. This is true particularly in evaluating programs of information dissemination, in assessing screening or early detection regimes or interventions that involve entire communities. Phase III research may involve the health-services-research analog of clinical trials in order to be fully assured that the proposed interventions are effective.

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Research Phases IV and V refer, respectively, to the evaluation of an intervention in a defined population, and of widespread application efforts. Defined populations are those so constituted that the results be extrapolated to the public at large, assuming a suitable delivery system for the intervention. The fifth phase involves the testing of demonstration and application efforts. Here the focus is on the delivery system for an already-proven intervention.

Prevention: Generally it is believed that prevention is the most cost-effective means of cancer control, namely that an ounce of prevention is worth a pound of cure. At the NCI we have focused on smoking and diet. In particular we have established a set of objectives, based on our current knowledge which if achieved would achieve major reductions in cancer mortality[2]. Over the next, 2, 5, or 10 years we may learn much that may cause us to modify these objectives but, in 1988, they reflect actions that, if applied prudently, will yield major reductions in cancer mortality.

Smoking is responsible for some 30% or more of cancer deaths. Eliminating smoking, all other factors remaining constant, eventually would reduce cancer mortality by 30% or more. Well-established facts relate smoking to cancer mortality and to mortality from other diseases and its deleterious impact on public health is clear and enormous.

Also, we have strong epidemiological, laboratory and animal evidence that diet plays a major causal role in cancer. We expect that current clinical intervention studies will coalesce with existing evidence to verify the prominent role of diet in cancer. Doll and Peto[1] summarized the state of information on cancer prevention in their study of the causes of cancer. They concluded that smoking and diet are principally responsible for the vast majority of cancer deaths. However, other causes, such as the environment and occupational exposures, also play a role, which may be quite significant in highly exposed persons.

Screening: Two sites dominate this area of control: cervix uteri and breast cancer. Many other sites have been discussed, but we have no definitive evidence to support their value in mass screening. The evidence for cervical cancer screening has been accumulated for the past 30 or more years. We have long believed that the Pap smear enables us to detect cervical cancer at a non-invasive and early stage. Evidence from public health trials in Scandinavian countries and elsewhere provides nearly conclusive proof that this technology is effective.

Breast-cancer screening has been tested more rigorously than that for cervical cancer; the former has been gathered in large-scale, well-controlled clinical studies[4,5]. Results from both studies make it clear that annual physical examination with mammography can reduce the mortality from breast cancer by at least 30% in women over 50. Indeed, the follow-up study of Health Insurance Plan (HIP) shows that screening women between 40 and 50 can also reduce breast cancer mortality[6].

Early Detection: The NCI has studied early detection in a wide variety of cancer sites. This can be done in physician's office during routine encounters with the patient, and at home. Screening is a more formalized mass activity, which may or may not involve a physician. The NCI has developed a set of early detection guidelines, which have been endorsed by the NCI's principal advisory body -- the National Cancer Advisory Board. These cover a wide range of cancer sites, including breast and cervix, as well as colon and rectal cancer, melanoma, testicular cancer, lung cancer, and prostate cancer. The purpose of the guidelines is to encourage responsible early detection for those cancers in which such detection appears to significantly improve prognosis.

In all of the cancer sites other than breast and cervix, we have no definitive evidence that we can reduce mortality by screening. However the circumstantial evidence -- namely the differential survival between early *versus* late stages for these cancer, and the effectiveness of techniques prescribed to detect the cancer has prompted the wide dissemination of these guidelines. We are developing methods to evaluate screening techniques for these cancers. Their relatively low incidence -- despite the large number of deaths attributable to them annually makes evaluation through prospective randomized clinical trials extremely costly and perhaps may not be feasible because of the large sample sizes required. However evaluation is mandatory and we are investigating the potential for case control studies and other designs. It is unfortunate that often we have to make recommendations based on incomplete information, however, NCI's guidelines represent a balance between the benefits indicated by the application of available knowledge and the potential risk of unknown or unanticipated costs or health outcomes.

Treatment and Rehabilitation: The past 20 years or more have seen significant improvements in treatment for a wide variety of cancer sites. These improvements have led to significant reductions in mortality. Data from the National Center for Health Statistics and the National Cancer Institute show significant reductions in mortality and improvements in survival for a number of different cancer sites for the period 1950-1985. Progress in treatment and/or early detection is reflected chiefly in those sites which show an excess reduction in mortality compared with the change in incidence: colon/rectal cancers, Hodgkin's disease, testicular cancer, the childhood cancers, and non-Hodgkin's lymphoma. A recent report (National Cancer Institute, 1988) outlines the reasons behind these changes. Note that, for cervical cancer, the change in mortality is approximately the same as change in incidence. One might conclude that a truly preventive regimen was at work here, however, the incidence has fallen because screening through Pap smears allows us to remove the cancer before it enters an invasive phase. The incidence figures noted here do not include in situ cervical cancers.

The figures suggest that advances in treatment reduce cancer mortality and that treatment is an important and effective means of cancer control. This conclusion is valid even if not all persons are receiving state-of-the-art treatment. While we have no comprehensive study of the treatment provided to all cancer patients, we do have figures showing substantial differentials in survival between blacks and whites, and in geographic areas where a high mortality is attributed to particular cancers. These differences may be explained by a lack of rigor in following cancer treatment protocols.

Predicting the Impact of Cancer Control Strategies

The methods used by the NCI to predict the impact of various cancer control strategies also have been applied to health systems[2,7-9]. In general, this operations-research-based strategy involves, as a first step, developing a model of the population showing how its demographics will change over time. These demographics include estimates of cancer incidence, survival, and mortality in the particular population under study, and cancer control programs already in place. The second step is to formulate and characterize the new cancer control program. This includes identifying the population(s) it may affect, the period when the program will be in operation, and the extent to which this program may affect the cancer experience of the affected population. Also it includes such factors as the delay in observing the change in one or more of the relevant cancer variables. The third aspect of the modelling is the valuation of the various outcomes and the cost of mounting the program.

The NCI has used these modelling techniques to analyze the potential impact of its cancer control objectives. The objectives relate directly to actions that can be taken to reduce mortality; these include smoking reduction, diet modifiction, breast and cervical cancer screening and the more extensive application of state-of-the-art treatment. Analysis leads to the estimate that eventually mortality could fall by 15% if the proportion of adults who smoke was reduced from approximately 32% to approximately 16%.

With respect to diet, the NCI estimates, conservatively, that mortality would be reduced by 8% if the population's fat consumption declined from 40% of calories to 30% or less and if fiber consumption increased to between 20 and 30 grams daily. Increased breast cancer and cervical cancer screening would achieve a 3% reduction in mortality. Finally, state-of-the-art treatment could achieve another 10% reduction. If cancer survival continued to increase as it has at approximately 0.5% per year, this 10% reduction could increase to 14% by the year 2000; if the rate of progress evidenced by changes in cancer survival increased to 1.5% per year, the reduction in mortality by the year 2000 from treatment could be as much as 26%.

Potential for Early Detection

Does detecting a cancer early improve a patient's prognosis? As noted earlier, we have firm evidence, at least in general terms, for only two cancer sites: breast and cervical cancer. However, there is considerable circumstantial evidence that early detection of colorectal cancers, melanoma, bladder and other malignant lesions may improve a patient's prognosis.

One can estimate the impact of early detection using a relatively simple approach based on the hypothesis that if, because of some intervention, a cancer is detected earlier, the patient's survival is that associated with the state of the cancer at this earlier detection time. Therefore the expected benefit of finding breast cancer in the regional, rather than in the stage of distant spread, can be expressed by the increase in 5-year relative survival between regional and distant disease. In numerical terms, the 5-year relative survival from "distant" breast cancer is 30% compared with 60% from regional disease, the difference represents increased length of life and an increased likelihood that treatment will cure the disease.

The NCI's Surveillance, Epidemiology and End Results (SEER) program provides measures of the survival associated with detection of particular stages of cancer and the percentage of patients detected with cancer in those stages. Also we can make a mathematical estimate of the relationship between survival and mortality rates for the cancer[9]. Now we need to estimate for these various cancers the change in the stage distribution due to early detection. The simplest model would assume that, for each stage of the disease, cancer control efforts would detect a fraction (p) of persons in the next earliest stage (of course patients who would have been detected in the earliest stage would undergo no change in prognosis -- they are still detected with first-stage disease). This type of analysis does not reveal the precise impact of early detection efforts; on the other hand, it does give, for various estimates of the parameter p, the order of magnitude of the impact of early detection efforts. Our estimate for the increase in survival for all sites combined is for each 0.1 increase in p, survival increases by 1.3 absolute percentage points, e.g., from 50 to 51.3% as p goes from 0 to 0.1. In general, finding the disease in an earlier stage if possible would revise 5-year relative survival from about 10% to about 65%.

It is clear from such an analysis that the impact of early detection may be considerable for many cancer sites. However, these estimates depend on the achievement of relatively high values of p -- realized through technological breakthroughs that will enable early detection of a particular cancer or through public information and dissemination programs. For some patients early detection means living with the knowledge of the cancer longer, even though there is no change in the length of the patient's life. We will learn the ultimate benefit from early detection only through careful evaluation but analyses can indicate those disease sites, which show the greatest potential benefit from early detection.

Progress to Date

In the United States over the past several decades, several cancers have shown considerable changes in mortality, or in mortality compared with incidence. For example, screening and early detection of cervical cancer have been quite effective in the United States. The incidence of cervical cancer and its mortality have fallen by more than 70% since 1950 (Table I). Public health officials attribute this almost entirely to widespread cervical screening. The most recent information from the NCI and the

TABLE I

Changes in Cancer Incidence and Mortality, 1950-1985 and 5-Year Relative Survival Rates, 1960-1984 Selected Sites, Males and Females

	All Races		Whites					
	Estimated Cancer Cases in 1985	Actual Cancer Deaths in 1985	% Change 1950-85				5-Year Relative Survival Rates %	
			Incidence		U.S. Mortality			
			Total	AAPC	Total	AAPC	1960-63	1978-84
All sites	910,000	461,520	36.5	0.8	6.7	0.2	39.0	50.1
All sites, excluding lung	766,000	339,125	22.6	0.5	-15.4	-0.5	. .	56.8
Oral and pharynx	28,900	8,290	-30.2	-1.0	-59.4	-2.4	45.0	53.5
Esophagus	9,400	8,612	-17.0	-0.6	0.0	-0.0	4.0	6.6
Stomach	24,700	13,949	-72.5	-3.6	-74.8	-4.1	11.0	15.7
Colon rectum:	138,000	57,586	18.6	0.5	-20.3	-0.6	42.0	53.3
colon	96,000	49,726	36.4	0.9	-0.1	0.1	43.0	54.2
rectum	42,000	7,860	-10.5	-0.3	-64.7	-2.8	38.0	51.5
Liver	13,400	5,952	. .	. .	-44.7	-1.9	2.0	3.4
Pancreas	25,200	23,099	18.2	0.4	19.3	0.3	1.0	2.7
Larynx	11,500	3,501	68.9	1.4	-12.2	-0.1	53.0	66.0
Lung and bronchus	144,000	122,395	238.6	3.2	246.5	3.3	8.0	12.9
males	98,000	83,754	212.8	2.7	228.4	3.1	7.0	11.6
females	46,000	38,641	432.4	5.3	447.2	5.4	11.0	15.5
Melanoma of skin	22,000	5,529	242.3	3.8	147.9	2.4	60.0	80.3
Breast (females)	119,000	40,090	43.6	0.9	4.4	0.1	63.0	75.0
Cervix uteri	15,000	4,508	-77.5	-4.0	-73.0	-3.8	58.0	66.7
Corpus and uteri, NOS	37,000	5,959	2.3	-0.0	-60.0	-2.4	73.0	83.3
Ovary	18,500	11,357	0.2	-0.1	-0.4	-0.2	32.0	37.3
Prostate gland	86,000	25,940	68.7	1.7	5.7	0.1	50.0	72.7
Testis	5,000	425	85.1	2.0	-60.0	-1.9	63.0	90.5
Urinary bladder	40,000	9,785	51.1	1.3	-32.7	-1.0	53.0	76.7
Kidney and renal pelvis	19,700	8,660	82.1	1.7	23.1	0.5	37.0	51.2
Brain and nervous system	13,700	10,265	. .	. .	46.9	1.0	18.0	22.9
Thyroid gland	10,600	957	83.6	1.5	-50.7	-2.0	83.0	92.5
Hodgkin's lymphoma	6,900	1,778	23.9	0.2	-61.0	-2.4	40.0	73.8
Non-Hodgkin's lymphoma	26,500	15,358	123.1	2.4	100.3	1.5	31.0	49.4
Multiple myeloma	9,900	7,819	178.7	2.2	194.4	2.5	12.0	23.9
Leukemia:	24,600	17,449	0.8	0.1	2.2	-0.2	14.0	32.1
acute lymphoma	3,085	1,419	. .	. .	. .	. .	4.0	48.1
chronic lymphoma	6,504	3,243	. .	. .	. .	. .	35.0	60.3
acute myeloid	6,480	4,948	. .	. .	. .	. .	1.0	6.9
chronic myeloid	3,405	2,164	. .	. .	. .	. .	12.0	21.9
all other	5,126	5,675	. .	. .	. .	. .	. .	17.2
Childhood cancers	6,000	1,840	31.9	0.4	-55.9	-2.3	28.0	63.1

Sources: Surveillance, Epidemiology and End Results Program, National Cancer Institutes of Health; American Cancer Society 1985 Cancer Facts and Figures.

AAPC = average annual percentage change;

. . = not available

National Center for Health Statistics[10] show that some 73% of women 40 and above have Pap smears at least every 3 years. Yet, in some areas in the United States the cervical cancer mortality rate remains high indicating that not all women take advantage of and/or have the opportunity for periodic screening. In co-operation with voluntary organizations and local public health officials, the NCI hopes to reach these groups in the near future so that all women can reap the full benefit of cervical cancer screening.

The results from breast cancer screening are more disappointing. Clinical trials have demonstrated that the mortality from this disease can be reduced by 30% or more in the various age groups. However, in the United States, there has been esentially no change in overall mortality in breast cancer over recent decades, even though the United States has made a concerted effort towards the early detection of breast cancer, and the lay press and television have emphasized the need for and the benefit of breast cancer screening. In the future, our behavioral survey may show a "payoff" in terms of an increase in breast cancer screening. During the period 1973-75, the great increase in detection of breast cancer was attributed to the publicity given to breast cancers of prominent women. Our incidence data showed an increase and subsequently a decrease for that time. We note, however, that the incidence figures have been increasing since 1976 without any real change in mortality figures. This may reflect somewhat earlier detection and increased screening although our behavioral data do not reflect this change in screening.

Our principal problem may not be only poor response. A recent survey by the American Cancer Society showed that many physicians do not believe that mammography is effective. Moreover, for most patients, primary care physicians are the first entry point into the health care system and it is critical that these physicians be convinced that a rigorous program of screening (or early detection) can achieve real benefits.

Thus in 1988, breast cancer screening remains a considerable challenge. Essentially we are screening the same percentage of women in 1970 as we screened in 1980. No doubt, this represents an increase in the number of women being screened but not an observable increase in the weight of screening. The NCI expects to increase its efforts in breast cancer screening in order to achieve a greater reduction in mortality in this, the number one cancer killer in women.

Conclusions

Our estimates of the impact of early detection, screening and treatment on cancer control suggest the following conclusions:

First, early detection and screening could have a major impact on the cancer statistics. However, it is extremely difficult to make a precise evaluation of the impact of early detection on cancer survival and mortality. Work now underway at the NCI concerning case control methods and assessment models may provide better evidence concerning the impact of prevention.

Secondly, the current situation -- *viz* a relatively low level of breast cancer screening across the United States, a high cervical cancer mortality rate in many groups of women, and the denial by some physicians that mammography is a valuable component of screening indicates that programs of prevention must surmount significant behavioral barriers if they are to achieve a full measure of screening.

Third, over the past 34 years, improved treatment has achieved considerable mortality reduction and has broadened the knowledge base upon which new treatments can be formulated There is every reason to believe that survival will continue to increase at a minimum rate of 0.5% per year and produce a considerable reduction in mortality by the turn of the century. Again, however, behavioral issues become paramount. In their practices, physicians must apply "the state of the art" and patients must be in a position to receive the best in cancer treatment. Thus, the NCI faces a major challenge as it searches for ways to encourage the health-care professional to apply the best treatments available.

Finally, we should set higher goals than simply looking at trends. In our cancer control programs, we believe we have set achievable objectives, but only if we achieve the necessary partnership between the relevant components of the health care system. The task is formidable but the gains will be truly significant.

We must also keep in mind the high costs inherent in any sort of disease-control programs. Also, these programs may lead to other diseases or health and social problems not contemplated in advance. We must think through rigorously the potential problems associated with control programs before these are put in operation. Also society must balance the economic costs against the benefits accruing from longer and more productive lives. In general, it is extremely difficult to estimate the costs of these programs because they can be formulated and delivered in a multiplicity in many ways. One of the roles of the NCI's Cancer Control Program is to determine the full range of benefits and costs associated with control programs drawing on the expertise of a broad range of scientists from medicine, the social sciences, and economics.

Early detection and treatment will save lives but we must identify and remove the barriers to effective cancer control. The Cancer Control Program of the NCI has undertaken this important task.

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REGIONAL CANCER CENTRES

OCF

REGIONAL CANCER CENTRES

The Ontario Cancer Foundation was established in 1943 by an Act of the Ontario Legislature to conduct a program of research, diagnosis and treatment in cancer. The Foundation works in three fields: service, research and education. From its inception, the Foundation has accepted responsibility for:

- the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or special facilities; and
- the maintenance and operation hostels in connection with its treatment centres.

The Foundation also has the most important duty of co-ordinating facilities for cancer treatment and ensuring the adequate reporting of cases and the recording and compilation of data.

The Foundation with its eight Regional Cancer Centres -- Hamilton, Kingston, London, Ottawa, Sudbury, Thunder Bay, Toronto-Bayview, and Windsor -- provide facilitics for undergraduate and postgraduate study, training of technical personnel, and research fellowships to increase our knowledge about cancer.

The Foundation is distinct from but co-operates with the Ontario Cancer Institute incorporating the Princess Margaret Hospital in the investigation and treatment of cancer and works closely with the Canadian Cancer Society Ontario Division.

The Foundation hopes that *Cancer in Ontario* will assist the practising physician in some of the following ways:

- help him/her become familiar with the various services of the Foundation and its Centres;
- encourage effective patterns of referral and to promote efficient geographical use of the Regional Cancer Centres;
- encourage the individual physician to consult informally with staff members at the Regional Cancer Centre;
- make the resources of the Foundation more widely available to the people of Ontario by increasing the number of contacts between physicians, particularly those outside metropolitan areas, and the OCI/PMH and the Foundation's Regional Cancer Centres.

We urge any physician who reads *Cancer in Ontario* to make suggestions concerning the improvement of cancer control in Ontario. These may be transmitted to the Director of the nearest Regional Cancer Centre or sent directly to the Executive Director, Dr. J.W. Meakin. The Directors of the Regional Cancer Centres may be contacted as follows:

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V.R. Basrur, Ph.D., M.D.
D.I. Hodson, M.B., B.Ch.
C.R. Johanson, M.D.
H. Lukka, M.B., Ch.B.
J. Sathya, M.B., B.S.
I.Z. Strautmanis, M.D.
A.A.M. Tadros, M.B., B.Ch.
A. Whitton, M.B., B.S.

Medical Oncologists:

A. Arnold, M.B., B.S.
G.P. Browman, M.D.
E. Chouinard, M.D.
A.T. Figueredo, M.D.
M.N. Levine, M.D.
P.B. McCulloch, M.D.
A.J. Neville, M.B., Ch.B.
J.J. Rusthoven, M.D.

Gynecologic Oncology:

G. O'Connell, M.D.

Physicists:

C. Kwok, Ph.D.
M. Patterson, Ph.D.
V.G. Peters, B.Sc.
R.H. Price, B.Eng.
B.C. Wilson, Ph.D.
D. Wyman, Ph.D.

Clinical Assistants:

H. Geffen, M.D.
M.D.E. Goodyear, M.B., B.S.
C. Jones, M.D.
E. Latimer, M.D.
M.E. McBride, M.D.
D. Nicholson, M.B., B.Ch.
C.L. Tanser, M.D.
D. Ward, M.D.

Career Scientists:

G. Singh, Ph.D.

Administrator: C.E. Squires	**Nurse Administrator:** G. Holmes-Brown, R.N., B.A.S.
Business Office Manager: C.F. Freeman, R.I.A.	**Cancer Information Service:** B. Rigby, B.Sc.N., M.H.Sc.
Senior Radiotherapy Technician: B.J. Walker, R.T.	**Manager of Health Records:** D. Armstrong

Lakeview Lodge Supervisor:
C. Stewart, R.N.

The year 1988 saw a number of changes at the Hamilton Regional Cancer Centre.

Dr. William Muirhead retired after more than 29 years of service to the Centre. Dr. H. Lukka has joined the staff as a radiation oncologist and Dr. J. Rusthoven has been appointed to the medical oncology staff. Mrs. Heather Porter left the Centre to return to university and, in her place, Ms. Gayle Holmes-Brown has been appointed senior nurse administrator.

The postgraduate training program in radiation oncology continues to expand under the directorship of Dr. A. Whitton. At present, there are five residents in training. The medical oncology program under Dr. A. Arnold has one resident.

The Community Cancer Clinic Network for Central-West continues to develop under the guidance of Dr. James Gowing. A request for funding of the network was submitted to the Ministry of Health in June 1988. This proposal has been submitted for independent evaluation and in early 1989 it will be forwarded with other proposals for cancer care to the Minister of Health for approval.

Dr. M. Smaosh, medical oncologist/hematologist, has joined the St. Catharines Clinic.

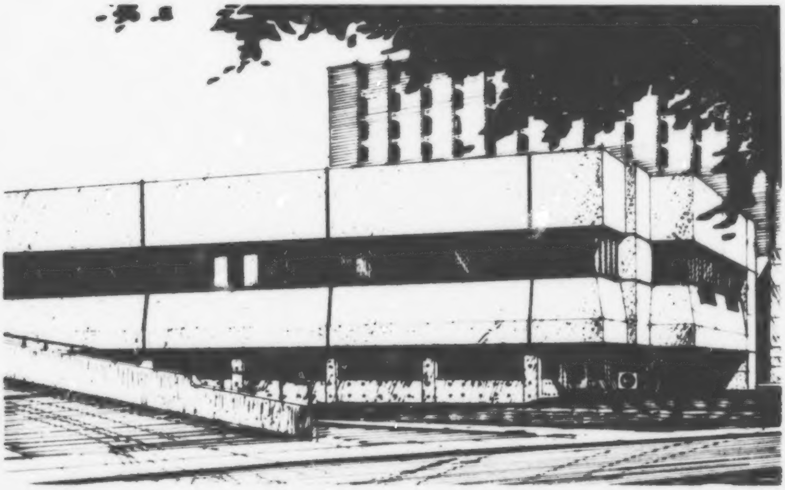
Research activity continues to have priority at the Centre: at present Centre staff hold 23 peer-reviewed grants. These diverse projects can be grouped under the following areas: 1) studies of new therapeutic modalities; 2) preventive and therapeutic clinical trials; 3) development of laboratory assays of therapeutic response; and 4) studies of the mechanisms of metastasis.

We continue to plan for the new centre and ground breaking is scheduled for August 1989.

B. Rigby, B.Sc.N., M.H.Sc.
Co-ordinator, Cancer Information Service

KINGSTON REGIONAL CANCER CENTRE

KINGSTON GENERAL HOSPITAL



Director:

A.D. Ginsburg, M.D.

Radiation Oncologists:

M. Brundage, M.D.
P.F. Dixon, M.B., B.S.
P.J. Froud, M.B., Ch.B.
V. Kraus, M.D.
W. Wells, M.D.

Medical Oncologists:

B.J. Campling, M.D.
E.A. Eisenhauer, M.D.
P.R. Galbraith, M.D.
W.S. Lofters, M.D.
J.L. Pater, M.D.

Clinical Assistants:

M.D. Mulligan, M.R.C.S., L.R.C.P.
P. O'Donnell, M.D.
D.C. Pross, M.D.

Career Scientists:

S.P.C. Cole, Ph.D.
J.S. Gerlach, Ph.D.
J.C. Kennedy, M.D.

Physicists:

J. Robins, M.A.
P.C. Shragge, Ph.D.

Honorary Medical Consultant:

R.C. Burr, M.D.

Administrator:

D.H.D. Steacy, B.A.

Head Nurse:

A. Voino, R.N.

Chief Technician:

N. Hobbs

Social Service Nurses:

R. Crafts, Reg.N.
C. Keith, Reg.N.

Manager of Health Records:

R. MacDonald, C.C.H.R.A.(C)

Quinte-Thousand Island Lodge Supervisor:

D. Broeders, Reg.N.

For the most part the past year has been a time of progress at the Kingston Centre.

Research is progressing on several fronts. Laboratory space in the Medical Sciences Building has been consolidated for basic oncologic research, and a critical mass is forming under the leadership of Dr. Roger Deeley -- Stauffer Professor of Cancer Research -- and with contributions from the OCTRF scientists: Drs. Barbara Campling, Susan Cole, William Mackillop and James Gerlach, Queen's University scientists, and National Cancer Institute of Canada (NCIC) scientists. We await major financial support for this group from these three agencies: this would only bode well for research and also for the present and future care of our patients. This year, Dr. Susan Cole won the prestigious Queen's University Basmajian prize for excellence in research.

Dr. James Kennedy continues his successful association with Prof. Roy Pottier at the Royal Military College; also he is working on several applied projects with residents and faculty from several Queen's University departments.

Following the appointment of Dr. Cliffe Lofters to our staff, entry of patients into clinical trials has increased significantly. Now we are contributing at a level appropriate to our designation as the NCIC Clinical Trials unit, especially with Drs. Joe Pater, Elizabeth Eisenhauer and Peter Dixon, "just around the corner".

Dr. W. Mackillop continues his innovative research into patient communication. This work may be well enough consolidated to survive his imminent departure to Edinburgh, where he will become Head of the Department of Radiation Oncology. Important liaisons have been established with the Department of Psychology (Julian Barling) and Psychiatry (Lynne Ginsburg and Paul Cameron).

A patient information centre, conceived and operated by Dr. W. Mackillop, Ed Osborne and a group of graduate students, is a great success as judged by patient satisfaction and care, and by the integration of the research group into the Centre.

In February, Dr. Woody Wells joined radiation oncology via PMH and

Stanford, and Dr. Michael Brundage will join in January 1989. At the moment, Michael is Chief Resident at PMH. Other superb additions to the Centre are Nancy Hobbs as Head Technologist, Rita Macdonald as Manager of Health Records, Ann Voino as Head Nurse, and Rob MacArthur as computer whiz. Indeed, it is the quality of individual staff memebers that determines the quality of a Centre -- we are well-served throughout the Centre! All Centre staff display a deep concern for the wellbeing of our patients -- an attitude that is reflected in a patient survey now underway.

Patient care has been significantly enhanced by the establishment of a Single Oncology Inpatient Unit in the Kingston General Hospital (KGH). Here, patients with cancer, whether admitted under radiation oncology or medical oncology, are nursed in the same unit by nurses with developing oncology expertise. Lucille Groll (KGH Department of Social Work) provides major support to the nurses on this unit through a weekly meeting. We expect that the appointment of a clinical associate to the unit will enhance patient care, with regard particularly to "symptom control" and emotional support, and also will improve nurse-physician communication. Another major event has been the appointment by KGH of Wesley Boston as Director of the Palliative Care Unit; already we have found pleasure and much profit from our work with him.

Multidisciplinary care has evolved further this year. Dr. Vera Kraus has organized conjoint skin cancer and neuro-oncology clinics, and is trying hard to develop similar breast cancer and lymphoma clinics. Surgical oncology in general is developing rapidly in Kingston under the guidance of Dr. John Carmichael (gynecologic oncology), with the enthusiastic support of Dr. Steve Hall (ENT), Dr. Charles Sorbie (surgery) and Dr. Al Morales (urology).

Pediatric oncology has been strengthened greatly with the appointment of Dr. Maryana Silva to the Departments of Medicine and Pediatrics, with a consultant appointment to our Centre.

Queen's University Nursing Faculty is launching a program in oncology nursing with the financial, moral and faculty support of the Hotel Dieu Hospital, the KGH, and our Centre. Ably advised by Ann Voini and Nancy Hobbs, from our Centre, Carolyn Baker (Queen's University Nursing) developed the course, which will be offered to nurses in the region. This combined venture illustrates the spirit of co-operation which exists among the various agencies in Kingston involved in the care of cancer patients. It is a great pleasure to acknowledge this spirit.

This year, a training program for radiation technologists has been launched under the aegis of Nancy Hobbs and Siobonne McArdle. A new vibrancy is reflected, also, in a new continued medical education program for the technologists, and a weekly inservice program for the nurses. Particularly pleasing, too, has been the co-operation of residents, technologists and nurses in presenting weekly cancer rounds.

Dr. Peter Dixon has developed a residency program in radiation oncology, which has been strengthened by the rotation through the Centre and through the Department of Oncology of family medicine residents. Dr. Peter Froud, Director of

CME at our Centre, is launching a major CME program with Dr. David Walker, Director of Queen's University CME.

It is also pleasing to record that Drs. Elizabeth Eisenhauer and Peter Froud were invited to discuss undergraduate oncology teaching at the recent Royal College meetings in Ottawa.

Again, despite shortages and restrictions, Dr. Peter Shragge and his group have been able to recruit good trainees to our clinical physics program, and to participate effectively in the Centre's overall training programs.

The climate of financial restraint and restriction is taking its toll. The staff, particularly Brent Bellamy, Rita MacDonald and Dot Broeders have been introducing some innovative economies. Despite these, however, we face serious problems. We struggle under an acute shortage of radiation technologists, and although we have a new simulator and a new linear accelerator, we operate these with too few staff. This state of affairs is unpleasant and risky for the patients, who have to wait too long before we start their therapy; also it is demoralizing for the staff. In a disease like cancer, which carries so much emotional overlay, this added strain is difficult to deal with. Other economies have a deleterious effect on nursing ratios, educational travel, computer development and research flexibility: taken together, they all have a cumulative, negative impact on staff morale and patient care.

In these tough times, it is my pleasure to acknowledge the administrative support, co-operation, wisdom and indeed, friendship of, among many others, Ken McGeorge, Barry Boardman, Peter Lewis, David Robertson and Loine Davis at the Kingston General Hospital, Hugh Graham at the Hotel Dieu Hospital, Duncan Sinclair (new Dean of Medicine), Larry Wilson (previous Dean), Stu Vandewater, Albert Clark and Bob Maudsley at Queen's University, and Dave Steacy, Paul Leplante, and Brent Bellamy of our own Administrative Office.

Finally, in this time of uncertainty and change, it is with deep satisfaction that I acknowledge the genuine support and understanding received from Head Office and from Dr. J.W. Meakin.

A. David Ginsburg, M.D., F.R.C.P.(C)
Director

OCF

LONDON REGIONAL CANCER CENTRE

VICTORIA HOSPITAL

London Regional Cancer Center

Director:

L. Levin, M.D.

Radiation Oncologists:

W.E.C. Allt, M.D.
P.J. Corbett, M.B., B.S.
A.R. Dar, M.B., B.S.
L.E. Gaspar, M.D.
J.A. Hammond, M.D.
A.L. Houghton, M.B., Ch.B.
A.T. Porter, M.D.
H.L. Pritchard, M.B., B.S.

Medical Oncologists:

V. Bramwell, M.B., B.S.
G. Cairncross, M.D.
W.I. Kocha, M.D.
R.C. Lohmann, M.D.
D. Macdonald, M.D.
W. Mertens, M.D.
J. Skillings, M.D.
A. Smith, M.D.

Physicists:

A. Akinradewo, Ph.D.
J. Battista, Ph.D.
D.J. Dawson, Ph.D.
J. Schroeder, M.Sc.

Career Scientists:

A. Chambers, Ph.D.
J. Harris, Ph.D.
W.R. Inch, Ph.D.
D.J. Koropatnick, Ph.D

Administrator:

M.J. Morrison, M.P.A.

Business Manager:

B. Hodgert

Nursing Services Manager:

W. Gillis, B.Sc.N.

Radiation Therapy Technology Manager:

P. deSilva, R.T.T.

Social Work Manager:

A. Sawarna, M.S.W.

Health Information Services Manager:

D.G.E. Ross, C.C.H.R.A.

Thameswood Lodge Manager:

C. Sellery, B.Sc.N.

On May 13, 1988, following three years of extensive planning, the staff of the London Regional Cancer Centre left its home of approximately 40 years and relocated to its new facility, perhaps one of the finest in Canada. The new Centre was fully operational within four weeks of relocation; the staff has worked with energy and enthusiasm to create a comprehensive cancer centre second to none. On June 10, Premier David Peterson opened the new Centre at a colorful ceremony attended by 500 guests and followed by a dinner/dance for 250. The Centre was opened to patients on May 17 and put on public display at an Open House on the weekend of the official opening. Some 2500 people attended.

While most of the past year was spent preparing for the relocation, we have worked to ensure that the soul of the new Centre is consistent with its beautiful environment. Disease site specific multi-disciplinary teams were set up before relocation and new communication techniques were used to ensure the best in patient care.

The London Regional Cancer Centre provides a solid base for a major research effort. All indications are that, during the next three to five years, our new cancer research laboratories will develop into an excellent institute comprising 10 laboratories. The Clinical Studies Unit, which will provide the backbone for excellence in clinical research, already is on a sound footing. Dr. Bramwell's interleukin-2 study has attracted attention across North America and the neuro-oncology program under Dr. Cairncross has reached national and international stature.

The recent appointment of Dr. Arthur Porter to the Department of Radiation Oncology, and that of Dr. Jerry Battista as chief physicist has generated new research effort in these two departments. The radiotherapy facilities at the new Centre represent state-of-the-art technology; for example, we have the world's largest screened operating room -- here intraoperative radiotherapy will become a major initiative.

An oncology education unit has been established, under the direction of Mrs. Shelley Markland. The London Regional Cancer Centre has the largest outreach program in the Province; reaching out to health-care professionals in southwestern Ontario to share our experience in cancer care. This program will be expanded to include guidance in screening and early detection following Canadian guidelines, wherever appropriate. We hope this effort will draw the London Regional Cancer Centre and the Canadian Cancer Society close together as partners in these areas. Analytical dietary intervention studies now are on a sound footing at this Centre, in large part to the participation of Mrs. Dianne Goettler.

This year, as part of our relocation, we have appointed many new staff. Space does not permit the mention of each by name; however, I would like to announce that Mrs. Brenda Hodgert is the new manager of the business office; Mr. John Paddon, the new computer supervisor; Miss Lisa Escaf, who played a major role in planning oru relocation, joined the administration team; and Drs. Laurie Gaspar and Wilson Mertens graduated from our residency programs to become staff radiation and medical oncologists, respectively.

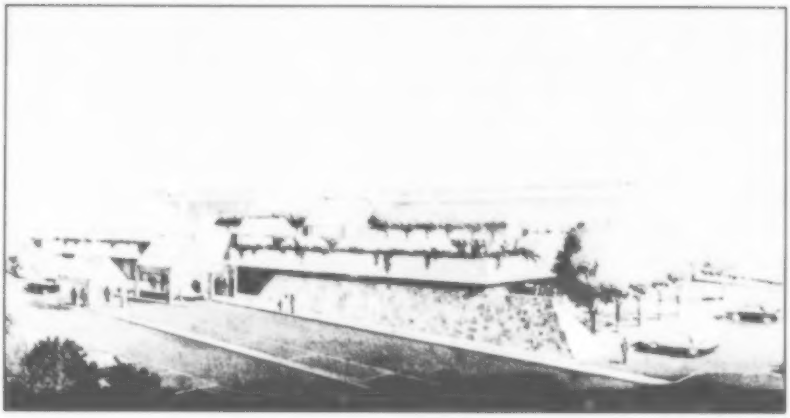
The operation of this new facility places a heavy but exciting responsibility on our shoulders. I am confident that this Centre will live up to its expectations, and make a major contribution to cancer care and control within the Ontario Cancer Treatment and Research Foundation.

L. Levin, M.D.
Director

OCF

NORTHEASTERN ONTARIO ONCOLOGY PROGRAM

LAURENTIAN HOSPITAL, SUDBURY



Director:

R.E.T. Corringham, M.B., B.S.

Radiation Oncologist:

R.J. Bissett, M.D.

Medical Oncologists:

T. Bozek, B.M., B.Ch.
G.D. Goss, M.B., B.Ch.
C.L. Sinoff, M.B., B.Ch
M.D. Vincent, M.B., Ch.B.

Clinical Assistant:

G.M. Kane, M.B., B.Ch.

Epidemiologist:

V. Nguyen, Ph.D.

Psychologist:

S. Steggles, Ph.D.

Nurse Administrator:

C. McChesney, B.Sc.N.

Manager of Health Records:

R. Zambelli, C.C.H.R.A.(C)

At the Northeastern Ontario Oncology Program (NEOOP) 1988 was a year of significant achievement but also considerable frustration.

Our clinical workload has doubled. Already this year the a clinical staff working in cramped quarters and with inadequate facilities has seen over 500 new patients. These difficulties will impede the expansion of service to people in the Northeast until the new Centre opens. Increased clinical activity has been matched by an increase in clinical trials; we have found funds for two clinical trials nurses who will assist our clinical trials co-ordinator. Because of a freeze in hiring, we have not replaced our clinical nurse teacher, which has set back our educational program, or hired a social worker to assist in developing our psychosocial program. Dr. Shawn Steggles, our psychologist, continues to work alone, and has taken on many of the tasks of a social worker. In a community with a large Francophone population, we need to develop bilingual services, particularly those of psychosocial support.

We now have a radiation oncologist, Dr. Randy Bissett, working out of the Princess Margaret Hospital in Toronto. He attends regular clinics in Sudbury and takes many referrals from the Northeast. In 1989 we hope to expand these multidisciplinary clinics into other northern communities. This year, NEOOP medical staff attended clinics in our sister centre in Thunder Bay when they had staff shortages; happily these now are largely resolved. We will continue this co-operation by collaborating in clinical trials.

In the coming year, we hope to recruit a clinician scientist and obtain funding to increase "wet-lab" research in collaboration with Laurentian University. In epidemiology, in a collaborative venture with the Thunder Bay Centre, we have expanded our research activities to encompass the whole North.

At the moment, construction of our Centre is at a standstill while we await the awarding by the Ministry of Health of the contract for final phase. It seems unlikely that the Centre will be completed before late 1990, or in operation before 1991 -- a year later than the original projection.

Vivian Cousins has joined us as charge nurse, and with other new NEOOP workers our staff now exceeds 50. We wish to congratulate Drs. Bozek, Goss and Sinoff on their success in various licensing and specialist examinations.

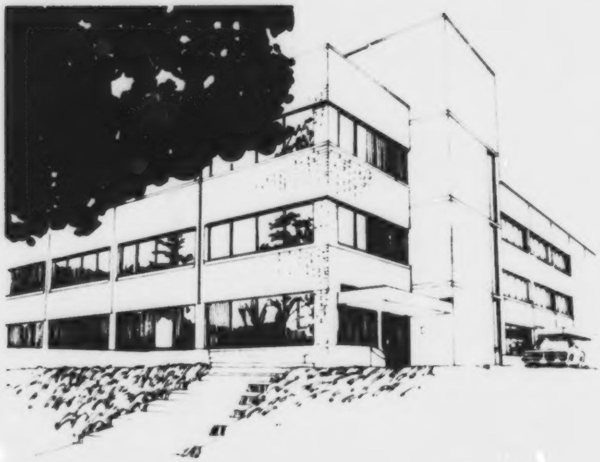
This year, despite delays and setbacks, NEOOP has made considerable progress in improving patient services and in establishing the infrastructure for a truly comprehensive regional cancer centre. These achievements reflect the enthusiasm, dedication and hard work by all members of the NEOOP staff. We look forward to greater progress in the new year.

R.E.T. Corringham, M.B., B.S.
Director

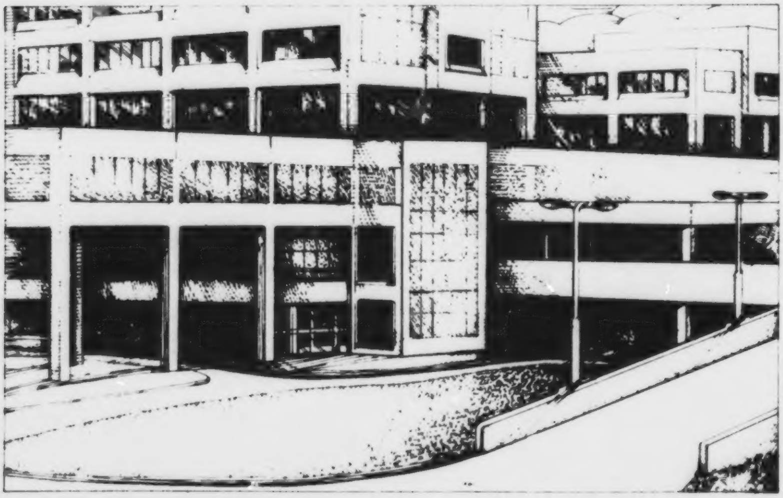
OCF

OTTAWA REGIONAL CANCER CENTRE

OTTAWA CIVIC HOSPITAL



AND OTTAWA GENERAL HOSPITAL



Director:

W.K. Evans, M.D. (July 1/88)

Radiation Oncologists:

J. Crook, M.D.
C.J.E. Danjoux, M.D.
L. Eapen, M.D.
B. Esche, M.D.
P. Genest, M.D.
A.L. Girard, M.D.
R.S.R. McDermot, M.D.
B.D. Nair, M.B., B.S.

Medical Oncologists:

S. Aitken, M.D.
C. Cripps, M.D.
D. Logan, M.D.
J.A. Maroun, M.D.
D.J. Perrault, M.D.
D.J. Stewart, M.D.
S. Verma, M.D.
V.P.J. Young, M.D.

Clinical Assistants:

H. Bastianelli, M.D.
J. Cinanni, M.D.
E. Grunfeld, M.D.
K.R. Hopkinson, M.D.
S. Langlois, M.D.
K. O'Toole, M.D.
I.A. Prosser, M.D.
K. Robillard, M.D.
S. Wong, M.D.

Career Scientists:

H.C. Birnboim, M.D.
R.G. Liteplo, Ph.D.
R. Hawley, Ph.D.

Physicists:

J. Cygler, Ph.D.
L.H. Gerig, Ph.D.
P.C. Johns, Ph.D.
R.M. Kroeker, Ph.D.
P.M. Pfalzner, M.Sc.
G.P. Raaphorst, Ph.D.
D. Salhani, Ph.D.
M. Soubra, M.Sc.

Administrator:

M.L. Trickey, M.B.A.

Business Manager:

S. McAdam

Executive Secretary:

D. Pineau, C.M.S.

Nurse Administrator:

C.J. MacMillan, B.Sc.N.

Head Nurse (General Division)

L. Fawcett, R.N.

Head of Radiation Technologists:

R.P. Wallace, A.C.(T)

Managers of Health Records:

Civic Hospital Division
S.A. Montgomery-Parsons, C.C.H.R.A.(C)
General Hospital Division
M.M. Brassard

Lodge Managers:

Maurice J.Grimes Lodge
J.M. Davidson, R.N.
Pavillon Alta-Vista Lodge
I. Martin, R.N.

A number of changes in key personnel have occurred during the past year. Dr. Gordon E. Catton retired after eight years as Director of the Ottawa Regional Cancer Centre. During that period the Centre witnessed a rapid growth in case load and service load at both of its divisions. Clinical staff were recruited to meet the service needs, strong experimental oncology and medical physics groups were set up, a Siemens KD-2 linear accelerator was placed at the General Division, a Cancer Lodge was built to serve the patients at the General Division and Lodge facilities were expanded on the Civic Hospital campus. These and other developments markedly strengthened the Centre and with the talents of its staff make it possible for the Centre to provide excellent patient care in a research environment. In addition to performing his administrative tasks, the new Director, Dr. W.K. Evans, expects to continue his clinical practice and his research related to lung cancer. A search is under way for a new Head of Medical Oncology for the Centre. Dr. Susan Aitken is the acting Head for the Civic Division. In parallel, we are searching for a new Head of Radiation Oncology for the Ottawa Centre to replace Dr. Gordon Catton.

Congratulations to Drs. David Stewart and W.K. Evans who were promoted to the rank of Full Professor of Medicine at the University of Ottawa. A number of trainees in the Ottawa program have completed their programs. Dr. Zeenat Y. Alam has completed her training in medical oncology and has accepted a position at the Windsor Regional Cancer Centre. In July, Dr. Barbara Fisher was awarded her Royal College Fellowship in Radiation Oncology and went to Stanford University Medical Centre on a Gordon Richards Fellowship to study hyperthermia under Dr. George Hahn. Dr. Adnan Ezzat, who completed his Royal College examinations in internal medicine and medical oncology, returned to Saudia Arabia and a post at the King Faisal Specialist Hospital. Dr. Laval Grimard, who also passed the Royal College examinations in radiation oncology, is continuing his studies in Paris.

Dr. Kathy Howard left the radiation oncology training program to direct the palliative care program at the Northeastern Ontario Oncology Program in Sudbury. The Ottawa Centre welcomes: Dr. Pierre Lefebvre -- a Clinical Fellow in Radiation Oncology; Drs. Michael Pereira, John Radwan and Salim Chammas to the radiation oncology training program; and Dr. Richard Gregg to the medical oncology training program. Drs. E. Grunfeld and S. Langlois have joined the staff as radiation oncology clinical asssistants replacing Drs. S. McKim and J. Blakslee.

In October 1987, three radiation technology students -- Manon Lasalle, Andree Cadieux, and Lilian Diotte -- graduated from the Centre's training program and were honored at a graduation ceremony. Manon Lacelle won an award at the annual conference of the Ontario Association of Medical Radiation Technologists for her essay "High LET Particles in Radiation Therapy".

The Centre's physicians participated in a number of national and international scientific conferences. Dr. W.K. Evans spoke at a conference in Florence, Italy, on screening in oncology "A Pilot Study of Lonidamine in Combination with Chemotherapy for Patients with Extensive Small-Cell Lung Cancer". Later in the year, Dr. Evans was invited to Perugia for the First International Cancer Conference which focussed on the current status of chemotherapy in non-small cell lung cancer. Here, Dr. Evans described the results of the National Cancer Institute of Canada's randomized controlled clinical trial of chemotherapy versus best supportive care in advanced non-small cell lung cancer.

Dr. Juanita Crook presented a poster entitled "Tailoring Radiotherapy to Reduce Complications in the Treatment of Cervical Cancer" at the First International Gynecological Oncology Society Meeting in Amsterdam. She made a presentation on "Conservative Treatment of Bladder Carcinoma by Combination Partial Cystectomy and Iridium-192 Implantation" at the American Society of Therapeutic Radiology Conference in Boston.

Several of the staff attended the annual meeting of the Royal College of Physicians and Surgeons in Winnipeg. Dr. Evans spoke to the Canadian Oncology Society on "A Phase II Study of VP-16 and Carboplatin in Previously Untreated Patients with Extensive SCLC". Dr. Cyril Danjoux -- a member of the Scientific Committee of the Royal College of Physicians and Surgeons -- chaired a seminar, and Dr. G.E. Catton chaired a symposium on manpower requirements.

The Ottawa Centre entertained many prominent scientists during the past year. Of note was the visit in June of Prof. Jean Papillon of Lyon, France, who was a guest lecturer to the Division of Radiaton Oncology. He spoke on conservative management of rectal and anal carcinoma and was well received.

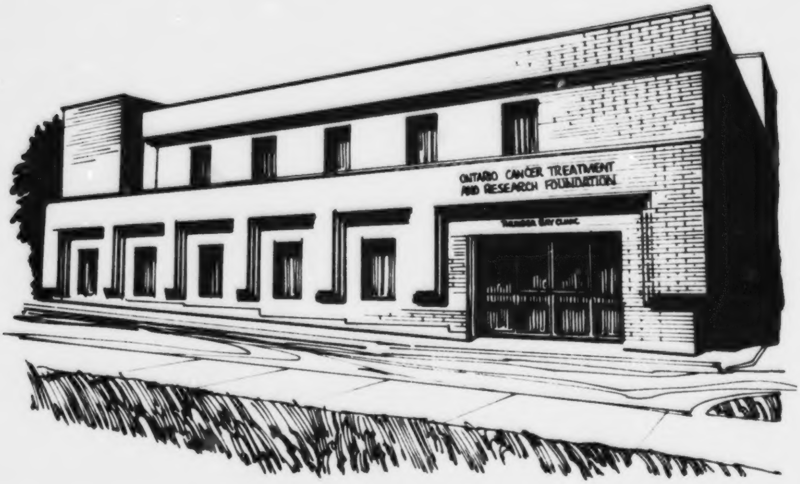
The career scientists of the Centre continue to obtain peer-reviewed funding. Dr. R. Liteplo, an associate investigator in experimental oncology, received a three-year award from the National Cancer Institute of Canada to extend his research into tumor progression and mechanisms of metastases.

In February, Ottawa achieved a national "first". Dr. Lothar Heubsch, a hematologist at the Ottawa General Hospital and a consultant to the Ottawa Centre, carried out a bone marrow transplant from an unrelated donor, with the support of the Division of Radiation Oncology. Dr. Cyril Danjoux supervised the radiotherapy of the four-year old boy who received the transplant.

W.K. Evans, M.D., F.R.C.P.(C)
Director

THUNDER BAY REGIONAL CANCER CENTRE

GENERAL HOSPITAL OF PORT ARTHUR


ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION
THUNDER BAY CLINIC

Director:
J.F. Kotalik, M.D.

Radiation Oncologists:
S. Gulavita, M.B., B.S.
M. McLean, M.B., B.Ch.

Medical Oncologist:
H.S. Dhaliwal, M.D.
H.L. Rayner, M.D.

Clinical Associate in Palliative Care:
J.A. Chalykoff, M.D.

Clinical Assistant:
L. Pratt, M.D.

Physicists:
M. Al-Ghazi, Ph.D.
B. Arjune, M.Sc.

Business Manager:
M.M. Ryan

Nurse Administrator:
L. Bright, Reg.N.

Manager, Radiation Therapy:
J.V. Morgan, R.T.

Manager of Health Records:
C. Alexson, C.C.H.R.A.(C)

Amethyst Lodge Supervisor:
M. Magnusson

Finally the year of 1988 has brought relief from the chronic shortage of staff at our Centre. Dr. Harry Rayner joined us as a medical oncologist after several years in private practice and service on the staff of the Manitoba Cancer Foundation in Winnipeg. Dr. H.S. Dhaliwal, who started earlier in 1987 as a locum medical oncologist and Visiting Professor at McMaster University, has accepted a full-time appointment as medical oncologist. Dr. Samuel Friedman from Institut Gustave Roussy in Paris did a locum in medical oncology and Dr. Crook from Ottawa helped in the radiation oncology department. Dr. Scott Sellick joined us as a clinical psychologist with a joint appointment to our Centre and Lakehead University; he will develop a research, educational and service program in psychosocial oncology. Mrs. Susan Fabius joined Mrs. Ann Roddy as a part-time pharmacist in our chemotherapy unit. On the other hand, we have lost the Head of our Department of Medical Physics, Mr. P.D. Sharma, who requested a long-term leave of absence to accept a position in the USA. For the past 17 years, Mr. Sharma has served this Centre and the Foundation and we greatly appreciate his important contribution to our advancement into modern radiotherapy. Until now the search for a new head of medical physics has been unproductive, but Dr. Matthew Al-Ghazi carries on capably as acting head. Also, we have lost two radiotherapy technologists who have yet to be replaced.

Our program of co-operative clinical trials is expanding under the leadership of Mrs. Eleanor Rayner, manager of the clinical trials unit and we are reporting on this in the Research Programs section of this publication. Our services were expanded further by the addition of community cancer clinics in Terrace Bay and Hearst; our previous clinics were in Fort Frances, Dryden, Sioux Lookout and Geraldton.

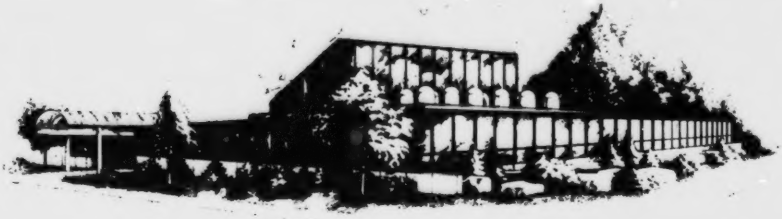
The major limitation to the growth and improvement in our services is a severe shortage of space. We have reached an agreement that a substantial fraction of our operations will be moved from the Centre's building into the lodge across the street after its basement is renovated. However, in spite of the climate of financial constraint, we have to proceed with planning for the expansion of the Thunder Bay Centre. Because of the severe shortage of beds in our host hospital and in Thunder Bay generally, we cannot get permission to start a special oncology unit in the hospital. However we will continue to optimize use of available space and beds until we are granted new funding for these programs.

J.F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

OCF

TORONTO-BAYVIEW REGIONAL CANCER CENTRE

SUNNYBROOK MEDICAL CENTRE



Director:

R.D.T. Jenkin, M.B., B.S.

Radiation Oncologists:

I. Ackerman, M.D.
J.M. Balogh, M.D.
M.P. Berry, M.B., B.S.
Ch.N. Catton, M.D.
P.A. Catton, M.D.
A.J. Dembo, M.D.
M.A. Doherty, M.B., B.S.
R.G. MacKenzie, M.D.
N.D. Mountifield, M.D.
G.M. Thomas, M.D.
C.S. Young, M.D.

Medical Oncologists:

N.L. Berinstein, M.D.
R.A.A. Buckman, M.B., B.Ch.
N.A. Iscoe, M.D.
I.J. Kerr, M.D.
K.I. Pritchard, M.D.
C.A. Sawka, M.D.
D.J.A. Sutherland, M.D.

Clinical Assistants:

H.M. Kocandrle, M.D.
H. Lau, M.D.
J.M. Wall, M.D.
J. Wong, M.D.

Physicists:

H.B. Michaels, Ph.D.
P.F. O'Brien, M.Sc.
R.A. Siwek, Ph.D.

Administrator:

H.B. Wodinsky, M.H.Sc.

Assistant Administrator:

N. Lowe, M.H.Sc.

Administrative Assistant:

K.A. Nicholson

Finance Manager:

A. Smith, B.A.

Nurse Administrator:

C. Johnston, Reg.N.

Chief Radiotherapy Technologist:
S.V. Scott, A.C.(T), R.T.R.

Manager of Health Records:
M. Mistruzzi, C.C.H.R.A.(C)

During 1988, the Toronto-Bayview Regional Cancer Centre (T-BRCC) continued its rapid growth. We anticipate that more than 4000 new patients (3500 new cancer patients) will be registered this year. The 1982 building, which was designed to serve 2500 new patients annually, has been outgrown and no space remains. Staff are being squeezed and pressured, bottlenecks develop and, for some services, patients wait for an unreasonable length of time. A functional program has been submitted to the Ministry of Health for the major expansion of this facility, which is essential if we are to serve the needs of 5000 new cancer patients (6000 new patients of all types), annually. We predict that this number will be reached in four to five years -- 1993 at the latest. The strategic plans of the OCTRF, the Fact Finders Report and the current Backley Committee all assume that this is the appropriate intermediate solution for Metropolitan Toronto. However our growth can be slowed only if in 1993 a third regional cancer centre for Metropolitan Toronto comes on line. The T-BRCC can support this marked increase in patient volume only if we have a major expansion before 1993. In October, the Ministry of Health approved funding for the first phase of this expansion and construction has started. A new 6 MeV linear accelerator and a second simulator will be installed in early 1989: Once this is done, the waiting time for simulation or treatment should be acceptable, at least for a year. We are "expanding" in the shelled-in space in the basement of the Centre that originally was to be "wet" lab research space. Completion of this project will cost three million dollars ($3M). We are greatly indebted to the Mayor and citizens of the City of North York who contributed $1M of this amount via a 0.5 mill tax levy on all households -- our Centre serves North York.

Failure to complete this laboratory research space earlier has been a major setback for this Centre but, in 1988, Sunnybrook Medical Centre elected to build a research tower adjacent to our Centre. Construction is underway and the building will be completed by the end of 1989. The OCTRF and the Ministry of Health have contributed $3M dollars towards the $16M cost of the first phase of this research tower. This building will house all wet-lab cancer research on Sunnybrook Campus, with advantages in terms of critical mass, scientific interaction and shared equipment. In 1988, our first physician/scientist, Dr. Neil Berinstein, arrived to initiate a laboratory program in biological response modifiers, initially at the downtown campus.

In 1988, the T-BRCC faces two mergers, that of the OCTRF and the OCI, and also the merger of Sunnybrook Medical Centre with the Wellesley Hospital. The latter calls for a major expansion of Sunnybrook Medical Centre and relocation of the Wellesley Hospital to this campus to create an acute-care facility with approximately 1150 beds. Thus the Bayview Campus of the University of Toronto's Faculty of Medicine enters upon a dramatic expansion: We anticipate approximately $333M of construction in the next five years. The doubling of the T-BRCC and creation of the University of Toronto's "Sunnybrook/Wellesley Health Sciences Centre" offers enormous advantages to both organizations.

During 1988, Dr. Alon Dembo became the Head of the Division of Radiation Oncology, an appointment that greatly strengthened multidisciplinary activities in gynecological oncology.

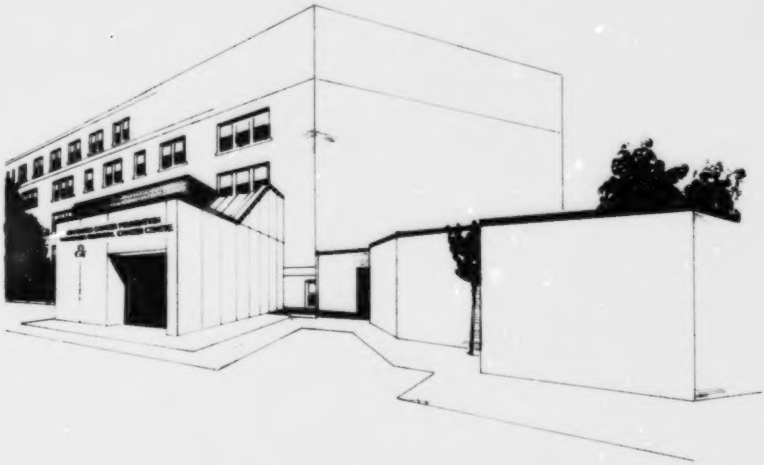
Harold Wodinsky, the Centre's administrator and chief operating officer, now holds the position of administrative co-ordinator of the comprehensive cancer program at the Bayview Campus. This appointment markedly enhances the co-ordination of our activities with Sunnybrook Medical Centre. Harold Wodinsky now spends half his time in each position. At the Centre, he is assisted by a new assistant administrator, Nina Lowe.

Thus 1988 has been a pivotal year in the history of the T-BRCC.

R.D.T. Jenkin, M.B., B.S.
Director

WINDSOR REGIONAL CANCER CENTRE

METROPOLITAN GENERAL HOSPITAL



Director:

G.C.K. Mok, M.D.

Radiation Oncologists:

J.A. Gilchrist, M.B., B.S.
L.F. Paszat, M.D.
C.D. Springer, M.B., B.S.

Medical Oncologists:

H.T. Abu-Zahra, M.B., B.Ch.
Z.Y. Alam, M.B.
D.A. Sicheri, M.D.
S. Yoshida, M.D.

Physicists:

M. Gribble, M.Sc..
D. Smocovitis, M.Sc.

Business Manager:

E. Hancock

Manager, Radiation Therapy:

M. Rice, A.C.(T)

Head Nurses:

R.A. Girard, Reg.N.
S. Vickers, Reg.N.

Manager of Health Records:

R. Van Der Borgh

In 1988 we had several staff changes: Dr. Larry Paszat, who practised radiation oncology at McGill University for the past three years returned to Ontario and became a staff radiation oncologist in our Centre in August of this year; Dr. Margaret Foote, clinical assistant, resigned in January and moved to North Carolina; Dr. Kaisiung Chang, medical radiation physicist, who joined our staff a year ago, returned to St. John's, Newfoundland, and his position was taken by Mr. Michael Gribble, who came to us from the London Regional Cancer Centre.

Mrs. Rita Macpherson Todd, senior radiation technologist, who retired in December 1987 was replaced by Ms Margaret Rice -- an experienced and capable person. She was chief technologist at the London Centre and at the Regina Cancer Centre before returning to Ontario. To ensure a supply of qualified radiation technologists in the future, we have started a radiation technologists training school at the Windsor Centre under the directorship of Ms Rice. Recently the authorities granted interim accreditation to 1990, at which time they will conduct an on-site inspection. Two young men are in our training program; they are enthusiastic and are making good progress.

Our dual-energy linear accelerator (SL25) went into clinical use in January of this year. On May 18, an Open House was held at the Centre to commission this machine and to dedicate the Mary Cooke Wing -- named in memory of the benefactor.

Now that we have more clinicians and have added skills in clinical research, we look forward to developing clinical trials using material available at the Centre. Also we plan to liaison with the Faculties of Nursing, and Biology and Physics at the University of Windsor. We will offer didactic and clinical programs to nursing students and will make available facilities in our radiation and physics departments for students instruction.

David Ng was an Ivan Smith Fellow in the Windsor Centre this summer. He received extensive exposure to both radiation oncology and chemotherapy during his stay. Under the guidance of the staff, David reviewed the treatment results and wrote a paper on medullary and inflammatory breast carcinoma.

As we have pointed out in the past, we have outgrown our facilities and can no longer meet the clinical and other demands made on the Centre. The new patient load has increased since our last expansion six years ago. The corridors in the Centre have become waiting areas. We do not have enough rooms for patient care and there is no space for new programs. As we anticipate the increase in patient volume projected by the Division of Epidemiology and Statistics, it is difficult to see how we can serve more patients in the present facilities. At present, we are leasing space off-site to house staff, equipment and records. Besides being expensive, the loss of any of these facilities would precipitate a crisis. Obviously, we will have to start planning today if we are to have a new Centre in the future. The longer we delay the worse it is for our patients.

G.K. Mok, M.D.
Director

SERVICE LOAD

The following tables describe the service load of the Foundation's seven regional cancer centres and the Northeastern Ontario Oncology Program in Sudbury during the calendar year 1987.

In 1987, 51,824 patients were seen at these centres. Of these, 92% had malignant lesions and, of these lesions, 15,487 were new to the centres (Table I). Of cases referred for non-malignant conditions, 83% were first seen in 1987 (Table II). The majority of the non-malignant conditions were seen for follow-up and consultation (1,537 and 470 respectively). In all, 11,192 malignant cancer cases were treated by radiotherapy (Table III); of these, 4,213 were treated by cobalt units, 5,195 by a linear accelerator, and 1,076 by other methods of radiotherapy.

During the year, patients made 523,014 visits to the regional cancer centres and the Northeastern Ontario Oncology Program, and the majority, 508,734, were for treatment of malignant disease (Table IV). Of all radiation treatments, 87% were given on an outpatient basis (Table V).

As of January 1, 1982, with the implementation of the Patient Care Management System (PCMS) in the centres, it has been possible to retrieve data in more detail than was possible in previous years. The current tabulations are taken from data as of August 1988. Consultation and follow-up visits have been divided and appear in separate columns in Tables I, II and IV. Simulations are shown in Table V but are not included in the totals. It must be emphasized that these tables are comparable only with the service load tables published for 1982, 1983, 1984, 1985 and 1986; they are not comparable with those for the years before PCMS was implemented.

TABLE I

Malignant Caseload During 1987*

TREATMENT CENTRE	TREATED				CONSULTATION ONLY	FOLLOW-UP ONLY	TOTAL
	Radiation	Radiation and Chemotherapy	Chemo-therapy	Procedures			
	Cases New in Current Year						
Hamilton	1,122	252	604	25	642	888	3,533
Kingston	520	139	125	28	187	257	1,256
London	1,016	283	378	131	544	699	3,051
Ottawa	1,037	269	423	107	394	697	2,927
Sudbury	–	–	179	4	61	69	313
Thunder Bay	212	37	76	11	72	131	539
Toronto-Bayview	1,040	225	221	422	331	589	2,828
Windsor	336	102	199	12	121	270	1,040
TOTAL	5,283	1,307	2,205	740	2,352	3,600	15,487
	Cases Registered in any Previous Year						
Hamilton	437	266	1,052	41	141	5,281	7,218
Kingston	202	109	259	26	117	2,386	3,099
London	358	229	593	208	257	4,366	6,011
Ottawa	403	342	995	154	71	6,162	8,127
Sudbury	–	–	168	4	8	172	352
Thunder Bay	76	43	166	21	31	1,007	1,344
Toronto-Bayview	240	150	309	138	97	2,101	3,035
Windsor	82	75	394	34	73	2,255	2,913
TOTAL	1,798	1,214	3,936	626	795	23,730	32,099
TOTAL ALL MALIGNANT	7,081	2,521	6,141	823	1,004	27,330	47,586

*Includes cases seen at peripheral clinics.

TABLE II

Other (Non-Malignant) Caseload During 1987*

TREATMENT CENTRE	TREATED				CONSULTATION ONLY	FOLLOW-UP ONLY	TOTAL
	Radiation	Radiation and Chemotherapy	Chemo-therapy	Procedures			
	Cases New in Current Year						
Hamilton	50	2	23	11	78	232	396
Kingston	3	1	77	90	102	283	556
London	43	1	47	529	109	341	1070
Ottawa	44	–	5	187	29	107	372
Sudbury	–	–	2	–	1	8	11
Thunder Bay	2	–	6	8	16	80	112
Toronto-Bayview	14	–	5	309	100	339	767
Windsor	14	–	13	32	35	147	241
TOTAL	170	4	178	1166	470	1537	3525
	Cases Registered in any Previous Year						
Hamilton	2	–	–	–	2	22	26
Kingston	1	–	1	–	2	33	37
London	2	–	–	1	2	60	65
Ottawa	2	–	1	25	3	68	99
Sudbury	–	–	–	–	–	–	–
Thunder Bay	–	–	–	–	–	10	10
Toronto-Bayview	1	–	3	52	11	377	444
Windsor	1	–	2	–	–	29	32
TOTAL	9	–	7	78	20	599	713
TOTAL ALL MALIGNANT	179	4	185	1244	490	2136	4238

*Includes cases seen at peripheral clinics.

TABLE III

Cases Treated During 1987 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO BAYVIEW	WINDSOR	TOTAL
	Malignant Neoplasms							
Superficial x-ray	162	214	137	15	24	56	87	695
Deep x-ray	1	5	–	–	–	–	14	20
Cobalt^{60}	1,268	444	586	1,242	188	700	493	4,921
Cesium^{137}	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–
Linear accelerator	837	435	1,514	1,098	223	1,088	–	5,195
Intracavitary	58	27	82	82	6	30	13	298
Interstitial	4	2	13	25	2	7	–	53
Moulds and applicators	–	–	3	–	–	–	–	3
Systemic isotopes	–	–	–	–	–	–	–	–
Others*	6	–	1	–	–	–	–	7
SUB-TOTAL	2,336	1,127	2,336	2,462	443	1,881	607	11,192
Simulations	2,774	1,283	2,462	2,930	446	2,444	1,283	13,622
	Other Non-Malignant							
Superficial x-ray	6	–	–	–	–	1	3	10
Deep x-ray	–	–	–	–	–	–	–	–
Cobalt^{60}	38	2	13	31	2	3	12	101
Cesium^{137}	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–
Linear accelerator	12	2	21	17	1	13	–	66
Intracavitary	–	–	–	–	–	–	–	–
Interstitial	–	–	–	–	–	–	–	–
Moulds and applicators	–	–	15	–	–	–	–	15
Systemic isotopes	–	1	–	–	–	–	–	1
Others*	–	–	–	–	–	–	–	–
SUB-TOTAL	56	5	49	48	3	17	15	193
Simulations	59	3	37	47	6	18	28	198
TOTAL**	2,392	1,132	2,385	2,510	446	1,898	622	11,385

*Others include radiation codes unknown.

**A case can be treated by more than one method per year. Simulations are displayed but are not included in the totals.

TABLE IV

Service Load, 1987*

TREATMENT CENTRE	VISITS FOR						TOTAL VISITS
	Treatment			Non-Treatment			
	Radiation	Chemotherapy	Procedures	Simulations	Consultations*	Follow-up Visits	
	Visits for Malignant Neoplasms						
Hamilton	29,562	17,811	362	2,774	5,723	39,222	95,454
Kingston	13,239	4,158	878	1,283	2,209	25,058	46,825
London	35,414	8,077	1,680	2,462	5,035	38,563	91,231
Ottawa	37,211	14,194	1,448	2,930	5,649	57,985	119,417
Sudbury	–	3,247	378	–	380	10,492	14,497
Thunder Bay	7,475	2,559	636	446	1,053	7,732	19.901
Toronto-Bayview	27,006	4,453	1,775	2,444	4,028	33,585	73,291
Windsor	10,729	6,205	407	1,283	1,582	27,912	48,118
TOTAL	160,636	60,704	7,564	13,622	25,659	240,549	508,734
	Other Non-Malignant						
Hamilton	525	85	55	59	238	548	1,510
Kingston	42	140	392	3	360	1,238	2,175
London	526	137	1,061	37	597	1,220	3,578
Ottawa	609	16	448	47	202	885	2,207
Sudbury	–	7	8	–	8	43	66
Thunder Bay	49	14	36	6	74	277	456
Toronto-Bayview	258	21	544	18	714	1,357	2,912
Windsor	236	43	111	28	169	789	1,376
TOTAL	2,245	463	2,655	198	2,362	6,357	14,280
TOTAL ALL VISITS	162,881	61,167	10,219	13,820	28,021	246,906	523,014

*Consultations includes reconsultations

TABLE V

Treatments by Radiotherapy During 1987, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO BAYVIEW		WINDSOR		TOTAL	
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
	Malignant Neoplasms															
Superficial x-ray	8	771	18	849	32	938	–	149	8	175	1	394	–	972	67	4,248
Deep x-ray	–	8	–	38	–	–	–	–	–	–	–	–	4	116	4	162
Cobalt^{60}	2,064	12,518	906	5,736	1,772	8,266	3,070	16,143	774	2,241	1,136	7,133	1,129	8,493	10,851	60,530
Cesium^{137}	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Linear accelerator	1,068	13,040	871	4,787	4,524	19,778	1,508	16,222	387	3,851	1,492	16,812	–	–	9,850	74,490
Intracavitary	74	–	32	–	88	–	94	–	6	–	31	–	15	–	340	–
Interstitial	4	–	–	2	5	8	25	–	3	–	7	–	–	–	–	–
Moulds and applicators	–	–	–	–	–	3	–	–	–	–	–	–	–	–	–	–
Systemic isotopes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Others*	5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SUB-TOTAL	3,223	26,337	1,827	11,412	6,421	28,993	4,697	32,514	1,178	6,267	2,667	24,339	1,148	9,581	21,161	139,443
Simulations	396	2,378	295	988	591	1,871	496	2,434	118	328	315	2,129	124	1,159	2,335	11,287
	Other Non-Malignant															
Superficial x-ray	–	56	–	–	–	–	–	–	–	–	–	10	–	14	–	80
Deep x-ray	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cobalt^{60}	1	243	–	5	–	144	–	283	–	45	–	34	12	210	13	964
Cesium^{137}	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Linear accelerator	–	225	–	36	32	335	25	301	–	3	–	214	–	–	57	1,114
Intracavitary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Interstitial	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Moulds and applicators	–	–	–	–	–	15	–	–	–	–	–	–	–	–	–	15
Systemic isotopes	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1
Others*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SUB-TOTAL	1	524	–	42	32	494	25	584	–	48	–	258	12	224	70	2,174
Simulations	1	58	–	3	2	35	–	47	–	6	–	18	2	26	5	193
TOTAL OF ALL TREATMENTS	3,224	26,861	1,827	11,454	6,453	29,487	4,722	33,098	1,178	6,315	2,667	24,597	1,160	9,805	21,231	141,617

*Others include radiation codes unknown.

CONSULTATIVE AND FOLLOW-UP CLINICS

The distribution of these clinics reflects the general zones of service of the Foundation's Regional Cancer Centres in Hamilton, Kingston, London, Ottawa, and Thunder Bay; and of the Princess Margaret Hospital, Toronto.

HAMILTON

Brantford	St. Joseph's Hospital
Burlington	Joseph Brant Memorial Hospital
Cambridge (Galt)	Cambridge Memorial Hospital
Guelph	Guelph General Hospital
Hamilton	McMaster Medical Centre and St. Joseph's Hospital
Niagara Falls	Greater Niagara General Hospital
St. Catharines	Hotel Dieu Hospital
Welland	Welland County General Hospital

KINGSTON

Trenton	Trenton Memorial Hospital

LONDON

Chatham	Public General Hospital
Kitchener	Kitchener-Waterloo Hospital
London	St. Joseph's Health Centre
Owen Sound	Grey-Bruce Regional Health Centre
Sarnia	St. Joseph's Hospital and Sarnia General Hospital
St. Thomas	St. Thomas-Elgin Hospital
Stratford	Stratford General Hospital
Wingham	Wingham and District Hospital
Woodstock	Woodstock General Hospital

OTTAWA

Cornwall	Cornwall General Hospital and Hotel Dieu Hospital
Ottawa	Riverside Hospital and Montfort Hospital
Pembroke	Pembroke Civic Hospital

THUNDER BAY

Dryden	Dryden District General Hospital
Fort Francis	Fort Frances Clinic
Geraldton	Geraldton District Hospital
Hearst	Notre-Dame Hospital
Sioux Lookout	Sioux Lookout General Hospital
Terrace Bay	McCausland Hospital

TORONTO

North Bay	North Bay Civic Hospital
Peterborough	St. Joseph's Hospital
Sault Ste. Marie	Plummer Memorial Public Hospital
Sudbury	Laurentian Hospital
Timmins	St. Mary's Hospital

CLINICAL CONSULTANTS AT THE OCTRF REGIONAL CANCER CENTRES AND THE PRINCESS MARGARET HOSPITAL

(As at December 31, 1988)

OCF Hamilton Centre:

M. Ali, M.D.
S. Archibald, M.D.
H.W. Beattie, M.D.
A.M. Benger, M.D.
W.F. Bennett, M.D.
I.W. Blackstone, M.D.
M. Brain, M.D.
P. Brown, M.D.
R.S. Bush, M.D.
A.J. Campbell-Moscrop, M.D.
B. Clark, M.D.
D. Clark, M.D.
J. Collins, M.D.
I.R. Davis, M.D.
P.B. Dent, M.D.
R. deVilliers, M.D.
B. Findlay, M.D.
J.D. Gowing, M.B., B.S.
R.A. Hadden, M.D.
J. Harvey, M.D.
D.A. Hitch, M.D.
B.S. Jackson, M.D.
P. Jenkin, M.D.
J. Kearns, M.D.
P. Knight, M.B., Ch.B.
J.A. McBride, M.B., Ch.B.
R. Meyer, M.D.
W. Nicholson, M.D.
S.E. O'Brien, M.D.
W.L. Orovan, M.D.
M. Rathbone, M.D.
W.D. Rider, M.B., Ch.B.
J.T. Roberts, M.B., Ch.B.
D. Rosenthal, M.D.
D. Sauder, M.D.
D. Savelli, M.D.
B. Trossman, M.D.
P. Vasarinsh, M.D.
I. Walker, M.D.
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1988 marked the 30th anniversary of the Ontario Cancer Institute incoporating the Princess Margaret Hospital (OCI/PMH). It was a year in which staff paused to reflect on past achievements and plan a future built on those accomplishments.

In February, we registered our 200,000 patient. In July, we welcomed Her Royal Highness, the Princess Margaret. For an anniversary reception, we located more than 30 of the original patients and welcomed the public to a large Open House on Sept. 25.

On Nov. 9, after a brief illness, Miss Phyllis Burgess, 71, who played a leading role in developing the specialized role of oncology nurses, died at Toronto General Hospital. Miss Burgess was the first Director of Nursing at Princess Margaret Hospital in 1957 -- a position she held until her retirement in 1977. Her experience with cancer patients stretched back to 1940 when she was night supervisor for the 50-bed ward for cancer patients at the Dunlap Building of Toronto General Hospital. In 1977, Miss Burgess was awarded a Civic Award of Merit by the City of Toronto for her outstanding contributions to oncology nursing and the care of cancer patients.

On Nov. 11, Mr. John F. Law died after a brief illness. To those on staff at OCI/PMH during the 1960s and early '70, Mr. Law will be remembered as the first Administrator. He built this hospital in the 1950s and took early retirement in 1974 to live a quiet life in the country. He was a kind and gentle man who knew that a building can be built with bricks and mortar, but that a great hospital can only be built when staff are allowed to grow to their full potential.

Throughout the year, staff contributed a great deal of time and thought to the development of the OCI/PMH's new functional program. This program required both an evaluation of current programs, staffing and needs, and the development of our vision for the future. Completed in the late summer, this document was delivered to the Ontario Ministry of Health in September. As the year came to a close, the architects, in consultation with our staff, had completed the basic block schematics for the new OCI/PMH.

Planning for a new institute is not done in isolation. The OCI/PMH has been part of the committee chaired by Mr. Alan Backley, to examine the ripple effect of our redevelopment on University Avenue on other hospitals and the University of Toronto. Through a number of subcommittees, the Committee has considered the extent to which our clinical and research programs can effectively interact with those of other institutions.

Also, the OCI/PMH staff have been exploring opportunities to participate in shared services and programs with the hospitals on University Avenue. In particular, we have co-operated with Mount Sinai Hospital, exploring the advantages of having two major oncology and research organizations next door to each other. During the coming year, we will continue to evaluate proposals for shared programs.

In parallel with our own plans, we have been developing oncology plans for the province as a whole. Throughout the year, the chairmen of the Boards of OCI/PMH and the OCTRF have discussed with the Ministry of Health and its consultants the development of a single cancer control agency for the province. The 1985 role study proposed this concept to co-ordinate provincial oncology programs, and to enhance future planning and resource allocation throughout the province. During the past year, the OCI/PMH and OCTRF Boards developed and approved a proposal to merge the boards of both organizations to form the Ontario Cancer Control Agency. This proposal awaits the Ministry's approval.

The clinical divisions have replaced some of their aging equipment. Last December, the new magnetic resonance imager went into service and this December the new Philips SL25 linear accelerator began treating patients. We plan to install four additional radiation therapy units in the basement of Mount Sinai Hospital. These machines, which will be ready to treat patients before the new OCI/PMH is completed, will be linked to the new building when it is finished. Although they will be housed in Mount Sinai Hospital, the facility will be managed and staffed by OCI/PMH.

During the year, Dr. Hugh Richmond became Chief of Pathology while Dr. Platts and Dr. Carruthers retired from that department. Dr. Izzie Boxen became head of nuclear medicine which joined radiology to form the Diagnostic Imaging Department under Dr. Steve Herman. In radiaiton oncology, Dr. F. Beale retired, Drs. A. Dembo and G. Thomas moved to the Toronto-Bayview Regional Cancer

Centre, and G. Rawlings left for England to further her education.

The high calibre of OCI/PMH research continues to be recognized in Canada and internationally. Among the many staff awards were Drs. Harold Johns (newly retired), E.A. McCulloch and Jack Cunningham. Dr. McCulloch, head of the biological research, received the Order of Canada for his contributions to both research and education. Dr. Harold Johns, known as "the father of the Cobalt machine", was featured on a commemorative stamp from Canada Post. Dr. Jack Cunningham became the second OCI/PMH staff member (in addition to Dr. Johns) to win the prestigious Coolidge Award from the American Association of Physicists in Medicine.

The teaching programs of the OCI/PMH were enhanced during the year. The School for Therapy Radiographers expanded its enrolment to meet the growing demand for therapy radiographers across the country. The OCI/PMH was awarded a five-year Terry Fox program and $600,000 for fellowships to encourage physicians to enter the Ph.D. program in medical biophysics.

Finally, it has been my great privilege to join the staff of OCI/PMH as the Director and Chief Executive Officer. The OCI/PMH has an enviable international reputation, and this is challenging and exciting time to work here, as together we develop and carry out our vision for the future.

Donald Carlow, M.D., C.C.F.P.
Director and Chief Executive Officer

TABLE I*

Number of Treatments Given in the PMH Department of Radiotherapy April 1986 - March 1988

EXTERNAL BEAM	1987-1988	1986-1987
Superficial x-ray	1,013	1,145
Deep x-ray	2,009	2,061
Cobalt	39,958	41,634
Linear accelerators:		
Low energy	8,433	8,652
High energy	26,986	28,567
TOTAL	78,399	82,059
Inpatient treatments	12,933	14,450
Outpatient treatments	65,466	67,609
TOTAL	78,399	82,059
SEALED SOURCES		
Intracavitary	235	274
Intrastitial (needles, wires and seeds)	32	30
Strontium	65	65
TOTAL	332	342

*Reprinted with permission, from the Ontario Cancer Institute's Annual Report for 1987-1988.

TABLE II*

Services Provided by PMH at Peripheral Clinics
April 1987 - March 1988

CLINIC	NEW PATIENTS SEEN	TOTAL VISITS
North Bay	97	1,260
Owen Sound	5	274
Peterborough	9	1,611
Sault Ste. Marie	37	658
Sudbury	3	1,061
Timmins	26	870
TOTAL	177	5,734

*Reprinted, with permission, from the Ontario Cancer Institute's Annual Report for 1987-1988.

TABLE III*

Cases of Malignant Disease
Distribution by Site of Malignancy and by Sex
April 1987 to March 1988

SITE	MALE	FEMALE	TOTAL
Head and neck	150	82	232
Ear, nose, throat	260	86	346
Gastrointestinal	441	269	710
Respiratory	627	317	944
Skin	318	251	569
Breast	5	1,201	1,206
Gynecological		620	620
Genitourinary	542	59	601
Lymphatic, hematopoietic	386	303	689
Other	306	261	567
TOTAL	3,035	3,449	6,484

*Data generated, with permission, from the Ontario Cancer Institute's Annual Report for 1987-1988.

TABLE IV*

New Patients with Malignant Disease
Distribution by Age and Sex
April 1987 to March 1988

SEX	0-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	TOTAL
Male	19	145	180	261	571	850	643	149	15	2,833
Female	32	131	290	488	663	868	553	177	23	3,325
TOTAL	51	276	470	749	1,234	1,718	1,196	326	38	6,058

*Data generated, with permission, from the Ontario Cancer Institute's Annual Report for 1987-1988.

SPECIAL SERVICES

PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources.

Drugs can be supplied only if attending doctors complete special prescription forms which are available from the Head Office, any of the Regional Cancer Centres, or the Princess Margaret Hospital. The completed form is mailed to the nearest Foundation centre or the Princess Margaret Hospital and the medication is mailed to the patient. The list of medications provided through the Foundation is available on request.

The total cost of the drug service in 1987 was $801,283.70 -- an increase of 5.4% from the $760,011.54 in the previous year (Table I). In 1987, 10,631 prescriptions were filled and the cost per prescription has increased to $75.37 from $70.96 in 1986.

TABLE I

Cost of Drug Service 1978-1987

Year	Payments for Drugs	Total Cost of Drug Service
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97
1982	370,388.28	375,971.20
1983	448,401.93	450,872.94
1984	569,966.52	572,300.25
1985	658,111.38	662,563.20
1986	756,111.56	760,011.54
1987	791,115.85	801,283.70

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for confirmed cases of cancer and the steroid-receptor assays for confirmed cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

Current scientific literature indicates that CEA determinations are useful primarily in patients with cancers arising from the large bowel, breast, or lung. The analytical materials available at present have little utility for tumors of other organs. The only exceptions are cancer of the cervix and medullary cancers of the thyroid.

During the fiscal period April 1, 1987 to March 31, 1988, 4,924 steroid-receptor assays and 50,913 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416) 521-2100 ext. 6293

Kingston General Hospital Dr. M. Raymond
Stuart Street
Kingston, Ontario K7L 2V7 tel: (613) 548-3232 ext. 4185

Victoria Hospital Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519) 432-5241

Ottawa Civic Hospital Dr. C. Lapkoff
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613) 725-4431

General Hospital of Port Arthur Dr. N. Escott
460 North Court Street
Thunder Bay, Ontario P7A 4X6 tel: (807) 343-6707

Sunnybrook Medical Centre Dr. A. Malkin
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416) 480-4648

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre Dr. E.D. Ryan
1200 Main Street West
Hamilton, Ontario L8S 4J9 tel: (416) 521-2100 ext. 6293

Victoria Hospital Dr. E.R. Tustanoff
375 South Street
London, Ontario N6A 4G5 tel: (519) 432-5241

Ottawa Civic Hospital Dr. T. Ooi
1053 Carling Avenue
Ottawa, Ontario K1Y 4E9 tel: (613) 725-4420

Sunnybrook Medical Centre Dr. D.J.A. Sutherland
2075 Bayview Avenue
Toronto, Ontario M4N 3M5 tel: (416) 487-2722

University of Toronto Dr. G.E. Mobbs
Medical Sciences Bldg., Rm. 7336
Toronto, Ontario M5S 1A8 tel: (416) 978-3553

DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1987, 6,178 specimens were submitted by dentists (6,313 in 1986).

The number of reports voluntarily submitted by the directors of pathology departments is approximately the same as in 1986, 65,000 reports.

These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation funds and administers seven lodges for out-of-town ambulatory cancer patients attending the regional cancer centres for diagnosis and treatment. These lodges provide comfortable, supportive accommodation, with minimal supervision, at no cost to the patient. When beds are available, escorts are accommodated at minimal cost.

The Foundation provides this accommodation because the patient often has to travel a considerable distance to reach treatment centres. Without these facilities, the patient would be admitted to hospital at far greater expense to the Province.

Shown below is a list of current facilities and number of beds:

		Number of Beds
HAMILTON	Lakeview Lodge	20
KINGSTON	Quinte-Thousand Islands Lodge	33
LONDON	Thameswood Lodge	50
OTTAWA	Maurice J. Grimes Lodge	60
	Pavillon Alta Vista Lodge	30
THUNDER BAY	Amethyst House Lodge	18
TORONTO	Princess Margaret Hospital Lodge	105

Patients who require hostel accommodation while being treated at the Toronto-Bayview Regional Cancer Centre are housed in a non-Foundation hostel facility.

The Maurice J. Grimes Lodge was expanded from 38 to 60 beds; the official opening took place on October 28, 1988.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation to any one of its regional cancer centres or to the Princess Margaret Hospital of those patients who live more than 25 miles from the centre and are considered to be in financial need. For patients 18 years or less, transportation is provided to the principal pediatric oncology treatment centres in the five health science complexes, namely:

HAMILTON	McMaster Medical Centre
KINGSTON	Kingston General and Hotel Dieu Hospitals
LONDON	War Memorial Children's Hospital, Victoria Hospital Corporation
OTTAWA	Children's Hospital of Eastern Ontario
TORONTO	Hospital for Sick Children

Usually transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1988, the total cost for transportation of patients was $712,647, compared to 695,730 for the fiscal year ended March 31, 1987.

CANCER INFORMATION SERVICE

In 1987, the Cancer Information Service began its second year as a province-wide program. The Service is funded jointly by the Ontario Cancer Treatment and Research Foundation and the Canadian Cancer Society Ontario Division.

The Service continues to use the most up-to-date cancer related data, and to provide modern, factual information on cancer and cancer-related resources. Our use of the Physician Data Query (PDQ) computerized database developed by the National Cancer Institute continues to increase.

Use of the Service is increasing: We receive, on an average, 500 calls per month.

Demographics remain basically unchanged. The largest group of callers are patients, family members and friends; 15-20% of inquiries are from patients, and 30-40% from family members and friends. Females continue to outnumber male callers 4 to 1.

We are developing research proposals aimed at several target groups.

User surveys indicate that respondents continue to be well satisfied with the Service.

Calls are answered Monday to Friday, between the hours 9:00 and 17:00.

RESEARCH PROGRAMS

SUMMARY OF OCTRF RESEARCH

PRESENT PROGRAMS

Career Scientists, Research Associates, Research Scholars and Clinician Scientists

During 1988, the Foundation provided salary and core support for 11 career scientists: Dr. G. Singh in Hamilton; Drs. S.P.C Cole, J. Gerlach and J.C. Kennedy in Kingston; Drs. A. Chambers, J. Harris, W.R. Inch and J. Koropatnick in London; and Drs. H.C. Birnboim, R.G. Hawley and R.G. Liteplo in Ottawa; 5 research associates at the University of Toronto: Drs. M.A. Baker, J.G. Connolly, B.L. Gallie, H.F. Haberman and G.E. Mobbs; and 2 research scholars: Dr. G.L. Hammond in London and Dr. J.C. Kudlow at the University of Toronto. The Foundation also provided core grants to cover such items as secretarial support and travel costs for three clinician scientists: Drs. D. Logan (Ottawa), B. Campling (Kingston) and N. Berinstein (Toronto-Bayview).

It is a pleasure to record that Dr. Susan Cole received the Basmajian Award for 1987-88. This award recognizes a young member of the Faculty of Medicine, Queen's University, who is "judged to have made the most meritorious contribution to medical research" during the previous year.

Senior Scientific Staff at the Ontario Cancer Institute

In addition to the funding of career scientists, research associates, research scholars and clinician scientists, the Foundation is the conduit through which the provincial government provides salary and core support for the senior scientific staff at the Ontario Cancer Institute. The annual research report of the Ontario Cancer Institute describes the projects carried out by these scientists.

The Division of Epidemiology and Statistics

The Foundation also supports members of the Foundation's Division of Epidemiology and Statistics in their research projects. Members of the Division, which has been affiliated with the Department of Preventative Medicine and Biostatics at the University of Toronto since 1978, compete for operating funds through the various external granting agencies. In addition to their individual research pursuits, they assist research workers throughout the Province by providing epidemiological and biostatistical information, by responding to requests from the Ministry of Health on relevant issues, and by providing information to the scientific community and general public.

The Ontario Clinical Oncology Group

Submitted by Dr. P.B. McCulloch

The Ontario Clinical Oncology Group (OCOG) was founded in 1983. Success has been achieved in the initiation and co-ordination of clinical trials and in the education of many new clinical investigators from the OCTRF regional cancer centres, the Ontario Cancer Institute and the Ontario medical schools.

The first, and largest, trial compares conservative therapy alone (lumpectomy) with adjuvant radiotherapy following the lumpectomy in surgically staged, pathologically node-negative, breast cancer patients. This trial, which was initiated in the spring of 1984, will close in December 1988 with a sample size of over 800 patients. As of September 1, 1988, 770 patients have been entered and followed for a median time of 26 months by investigators at Princess Margaret Hospital (Toronto), and the OCTRF Regional Cancer Centres in Hamilton, London, Ottawa, Thunder Bay and Windsor. Since accrual has been good, interested investigators are planning an additional trial of therapy in Stage I, breast-cancer patients.

A trial in a group at higher risk (Stage II breast cancer) was initiated in 1984 and closed in May 1987 (430 patients entered). The results of this trial of two different types of adjuvant chemotherapy have been published. Papers have also been published concerning incidence of thrombosis and quality of life in this group of patients.

This trial was followed by a dose-finding study for the combination of 5-FU, epirubicin and cyclophosphamide in a group of Stage II patients. To date, 71 patients have been registered from five regional cancer centres. The results from this pilot study will be used in planning another, full-scale, randomized trial.

The chemoprophylaxis of lung cancer is being studied. Just over 100 volunteers have been accrued into a randomized, double-blind study of etretinate -- a Vitamin A derivative. The investigators are attempting to reverse the metaplasia detected in the sputum of long-term cigarette smokers. The subjects are being recruited with the help of the Hamilton and Toronto-Bayview centres.

The value of medroxyprogesterone and wide-field radiotherapy is being studied in high-risk, localized endometrial cancer. This multi-centre trial was initiated in the spring of 1988 with participation from the OCTRF Centres at London, Toronto-Bayview, Hamilton, Windsor, Thunder Bay, Sudbury and Ottawa, and from the Ontario Cancer Institute. A total of 340 patients will be accrued over a four-year period.

In October 1988, the fourth annual three-day workshop on clinical investigation was held in the Department of Clinical Epidemiology and Biostatistics at McMaster University. Twenty participants registered from the OCTRF regional cancer centres, the Ontario Cancer Institute and Ontario medical schools. Each year, three tutorial groups put forward a number of research ideas and these are discussed in detail. Each of the three previous workshops have developed at least one research question to appoint where a participant could obtain peer-obtained funding from a national granting agency to carry out a clinical investigation. This enjoyable education experience has furthered the scientific career of many of the participants.

On September 20, 1988, Dr. Judith O'Fallon of the Mayo Clinic and Dr. Joseph Connors of the Cancer Control Agency of British Columbia carried out a site review of OCOG at McMaster University. The site visitors described OCOG as a strong program that merited continued support. We have made an application for renewal of OCOG support to the new Health System-Linked Research Units Program of the provincial government.

FUTURE POLICY

In the period June to November 1988, the Foundation's Research Advisory Panel received reports of present research activities and aspirations for future research from each of the eight regional cancer centres and from the Division of Epidemiology and Statistics. From these reports, the Research Advisory Panel will prepare a plan for future research support that will be discussed in detail with the directors of the regional cancer centres.

During 1988, the Foundation has pursued successfully its policy of producing a critical mass of researchers through co-operation between the regional cancer centres and the local universities and/or university hospitals at all of the regional cancer centres. A detailed review of this activity will form the basis of next year's report.

J.C. Laidlaw, M.D.
Director of Research and Education

RESEARCH PERSONNEL SUPPORTED BY OCTRF

Career Scientists

Hamilton Regional Cancer Centre:

G. Singh, Ph.D.

Kingston Regional Cancer Centre:

S.P.C. Cole, Ph.D.
J.H. Gerlach, Ph.D.
J.C. Kennedy, M.D.

London Regional Cancer Centre:

A.D. Chambers, Ph.D.
J. Harris, Ph.D.
W.R. Inch, Ph.D.
D.J. Koropatnick, Ph.D.

Ottawa Regional Cancer Centre:

H.C. Birnboim, M.D.
R.G. Hawley, Ph.D.
R.G. Liteplo, Ph.D.

Clinician Scientists

Kingston Regional Cancer Centre:

B. Campling, M.D.

Ottawa Regional Cancer Centre:

D. Logan, M.D.

Toronto-Bayview Regional Cancer Centre:

N. Berinstein, M.D.

Research Associates

Toronto General Hospital:

M.A. Baker, M.D.

Toronto Western Hospital:

H.F. Haberman, M.D.

University of Toronto:

J.G. Connolly, M.D.
B.L. Gallie, M.D.
G.E. Mobbs, Ph.D.

Research Scholars

University of Western Ontario:

G.L. Hammond, M.D.

University of Toronto:

J.E. Kudlow, M.D.

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Hamilton Regional Cancer Centre

DIFFERENTIAL EFFECT OF CISPLATIN ON MITOCHONDRIAL DNA IN THE MOUSE LIVER AND KIDNEY*

G. SINGH**, *Hamilton, Ontario*

Various studies have confirmed that cisplatin damages the nuclear genome, but little is known about the effects of the drug on the mitochondrial genome (mtDNA). It is reported that mtDNA may be an important target for several known carcinogens and mutagens. In these studies, we examined the effect of cisplatin on mtDNA in the liver and the kidney, because the drug induces toxicity in the kidney but not in the liver.

Mice were treated with various doses of cisplatin and groups of mice were sacrificed at different time points. Liver and kidneys were removed for isolation and analysis of mtDNA with specific mtDNA probes. These experiments were carried out to obtain both a dose-effect and a time-effect relationship on mtDNA in the hepatic and kidney tissue.

Our data showed a dose-related decrease in mtDNA in the kidney, but an opposite effect in the liver. It seems that mtDNA in the kidney and liver are regulated in an organ-specific manner after cisplatin treatment. This differential organ regulation could be due to hormonal influences following cisplatin-induced stress on the liver but not the kidney. Thus, it seems that the liver is protected from cisplatin injury by its ability to induce mtDNA synthesis during chemical stress, but the kidney does not have this protection.

This project is supported by a grant from the Medical Research Council of Canada.

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*CS-106-4.

**Career Scientist, OCTRF Hamilton Regional Cancer Centre; and Assistant Professor of Pathology, McMaster University, Hamilton.

ADDITIONAL INVESTIGATIONS

Dr. W.M. Hryniuk, Director of the Hamilton Regional Cancer Centre, reports on the following clinical research investigations:

RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF 5-FLUOROURACIL INFUSION CONCURRENT WITH RADICAL RADIATION IN ADVANCED SQUAMOUS CELL, HEAD-AND-NECK CANCER

Investigators: G.P. Browman, I. Hodson, M.L. Levine, C. Cripps and L. Eapen

The purpose of this study is to determine whether the addition of infusional 5-fluorouracil (5-FU) during weeks 1 and 3 of radical radiation improves survival in Stage III and Stage IV squamous cell, head-and-neck cancer. Patients meeting the eligibility criteria are randomized to 5-FU or placebo infusions. The study includes the development and validation of a new quality-of-life measure to obtain quantitative data on toxicity induced by radiation in these patients. The study is supported by a peer-review grant from the National Cancer Institute of Canada and, since April 1, 1987, 50 patients have been randomized. Preliminary assessment of the new head-and-neck questionnaire indicates that this instrument may be responsive to change and may detect clinically important differences in toxicity when radiosensitizers are added to radiation.

TUMOR PROLIFERATIVE INDEX IN HEAD-AND-NECK CANCER

Investigators: G.P. Browman and A. Kanclerz

This project, funded by the Ontario Ministry of Health, is designed to determine the prognostic relevance of tumor-growth fraction in squamous-cell, head-and-neck cancer. We are assessing two variables of growth fraction: the DNA-synthesis-labelling index using bromodeoxyuridine, and total tumor-growth fraction using a monoclonal antibody (anti-PAA), which is expressed in all cycling cells. To date, we have established a dose/response relationship between concentration of bromodeoxyuridine and labelling index; also we have done a formal comparison of the bromodeoxyuridine, tritiated thymidine and tritiated-deaxyuridine-labelling indices, which indicate the superiority of the BRDU labelling index. The anti-PAA technique has been developed in patients with squamous-cell, head-and-neck cancer. Also we have developed an image-analysis computer system, which can assess quantitatively the intensity of labelling of BRDU and PAA-stained cells. Samples are now being screened and the data will be correlated with clinical outcome.

RANDOMIZED TRIAL OF ERETINATE VERSUS PLACEBO TO REVERSE BRONCHIAL ATYPIA IN HEAVY SMOKERS

Investigator: A. Arnold

There is considerable evidence from experimental and epidemiological studies that Vitamin-A-like substances may protect against cancer. We are conducting a randomized trial looking at the efficacy of a synthetic retinoid in reversing sputum atypia in heavy smokers. The study, which is supported by a grant from the Ontario Ministry of Health, is entering its third year. To date over 100 heavy smokers with mild, moderate, or severe atypia have been randomized to receive etretinate 25 mg p.o. daily or placebo. The subjects are followed for six months and sputum samples are collected monthly.

No interim analysis was planned, therefore no results are available at the present time. The study has generated interesting data on the recruitment process itself and on the accuracy of sputum diagnosis.

We plan to continue this research and to refine our techniques for determining the outcome of treatment. Results from the overall trial should be ready in one year.

DETERMINANTS OF RESPONSE IN ACUTE LEUKEMIA

Investigator: G.P. Browman

This study, funded by the National Institutes of Health, hopes to identify clinical and laboratory prognostic variables in acute leukemia. The Hamilton Regional Cancer Centre is one of a consortium of institutions established in 1980 to co-ordinate laboratory studies and clinical data in studies of acute non-lymphocytic leukemia. Approximately 30 patients per year from Hamilton are entered into this study. To date, the consortium has identified several laboratory variables including cell kinetics, which influence remission rate. Among the clinical variables, the rate of cell kill following chemotherapy as judged by the appearance of the day 6 bone marrow is an important prognostic value. We will base future studies on these observations.

OCTF

Kingston Regional Cancer Centre

PHOTOCHEMOTHERAPY*

J.C. KENNEDY**, R.H. POTTIER† and P.C. SHRAGGE‡
Kingston, Ontario

These studies, which are designed to identify photosensitizing agents for the detection and treatment of cancer, consist of an integrated series of projects. These begin with basic studies of selected aspects of the physical chemistry and photochemistry of certain groups of chemically related photosensitizing agents. We selected for additional biological and photobiological studies, both in vitro and in experimental animals, compounds that have appropriate excitation spectra, that are efficient generators of singlet oxygen, and that have pH-dependent ionization and solubility characteristics such that they might reasonably be expected to accumulate preferentially in malignant tissues. These screening tests, which include studies of toxicity, neurotoxicity, tissue distribution, tissue clearance rates, cellular and intracellular patterns, and therapeutic effectiveness, are carried out in association with selected students and residents. Compounds, which pass this screen, may be selected for evaluation via clinical trials: First in pet dogs and cats that have developed spontaneous cancers; then in selected human cancer patients. At present, only one new compound has passed all of the preclinical screening and is undergoing clinical evaluation in patients. Finally, we are developing an attachment for adapting standard bronchoscopes, cystoscopes, etc., to detect and analyze tissue fluorescence as an aid to the identification and localization of very early cancer.

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*CS-101-1.

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MULTIDRUG RESISTANCE: MOLECULAR INTERACTIONS*

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Multidrug resistance (MDR) continues to be a major limiting factor in the chemotherapy of tumors. The studies being conducted in this laboratory will help provide an understanding of MDR mediated by P-glycoprotein. This high-molecular-weight, plasma-membrane glycoprotein is believed to function as a pore-forming, drug-export pump. Resistance results from a lower intracellular drug concentration in cells overexpressing P-glycoprotein. The specific goals of the research are:

1. *Generation of P-glycoprotein structural mutants.* Select multidrug-resistant variants of human tumor-cell lines are treated with mutagens to identify point mutations in P-glycoprotein. Such mutations will provide information on the structure/function relationships of the P-glycoprotein molecule and provide a basis for site-directed mutagenesis to probe fine structure.
2. *Construction of a P-glycoprotein expression vector.* The final characterization of the P-glycoprotein mutants will require that the cloned gene be expressed in a mammalian cell line. A full-length P-glycoprotein cDNA, which is being cloned, will be used to construct a mammalian expression vector.
3. *Detection of P-glycoprotein interactions in the plasma membrane.* Two approaches are being followed: (i) "cross-linkers" are being used to look directly for molecules associated with P-glycoprotein in the plasma membrane; and (ii) we are generating revertants of multidrug-resistant cell lines to identify "suppressor" mutations in proteins, which interact with P-glycoprotein.

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MULTIDRUG RESISTANCE IN HUMAN LUNG TUMORS*

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Small-cell lung carcinoma (SCLC) is one of the few solid tumors which initially is responsive to chemotherapy. However, the disease invariably recurs and, in the vast majority of patients, develops multidrug resistance (MDR). Overexpression of P-glycoprotein, a plasma-membrane protein, which functions as an efflux pump to reduce drug accumulation in the cell, has been detected in a number of different malignancies, but not in SCLC patients. This raises the possibility that, in this disease, MDR develops by non-P-glycoprotein-mediated mechanism(s). We have isolated, and partially characterized at the cellular level, a stable human MDR SCLC cell line, designated H69AR, in which we can detect no expression of P-glycoprotein. Also we have developed monoclonal antibodies (MAbs) which recognize epitopes in AR cells and two other MDR cell lines. The overall focus of our research is to investigate the cellular and molecular basis of drug resistance in the H69AR cell line.

This project is funded by the National Cancer Institute of Canada, the Ontario Thoracic Society, the Cancer Research Society, and the Clare Nelson Bequest of the Kingston General Hospital Inc.

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*CS-107-1.

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IN VITRO CHEMOSENSITIVITY TESTING OF HUMAN TUMORS*

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The ability to predict the response of human tumors to chemotherapeutic agents would have a major impact on the practice of oncology. Several methods have been used to measure the drug sensitivity of human tumors, but because of many practical limitations, none of these assays have improved our management of cancer. The major focus of my laboratory is the adaptation of a short-term cytotoxicity test -- the MTT assay, for clinical chemosensitivity testing. This simple colorimetric assay of cell survival and proliferation has many potential advantages over the other assays of cytotoxicity. It is rapid, simple, automated, and requires no washing steps, and no radioisotopes. The data obtained are precise and reproducible. The assay can be used with relatively small numbers of cells, and a single cell suspension is not absolutely required.

Using the MTT assay, 25 different chemotherapeutic agents have been tested for cytotoxicity to human tumor cell lines and fresh clinical samples. All but five of the drugs were active in this system. Because the assay is so simple to perform, it is possible to test multiple agents, each at several concentrations, on a single patient sample. We have performed multidrug chemosensitivity testing on a variety of clinical samples, including 18 leukemia specimens, 5 samples from small-cell lung cancer patients (including 2 lymph node biopsies and 3 effusions), 5 malignant effusions, and 3 miscellaneous solid tumors. In addition, we have established a panel of 12 small-cell lung cancer lines from patients at the Kingston Centre, and have tested each of these lines against a panel of 15 different chemotherapeutic agents. In doing this, we have been able to define the usual ranges of sensitivity to these agents, to compare the drug sensitivity of the cell lines, and to relate this to the treatment history of the patients from whom the cell lines were derived.

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COMPARATIVE STUDIES OF THE BIOCHEMICAL ACTION OF MENOGARIL AND ADRIAMYCIN ON CELL MEMBRANES*

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London, Ontario

Chemotherapeutic agents used in conjunction with other cancer treatment modalities have greatly improved the treatment of cancer. However, many of these agents have serious and toxic side effects, which limit their use. Menogaril, a promising new semisynthetic anthracycline, shows a decreased cardiotoxicity -- a major problem with the widely used anthracycline, Adriamycin. Structurally, Menogaril shows the same tetracyclic, anthraquinone-containing ring system but also it contains numerous structural differences, specifically the absence of an ionizable amino sugar moiety, and the presence of a glucopyranose attached to the D ring. Unlike Adriamycin, Menogaril binds weakly to DNA, inhibits RNA and DNA synthesis less, and shows different cell-cycle, and phase-specific toxicity[1]. These biochemical differences indicate mechanistic differences in modes of toxicity between Adriamycin and Menogaril.

Our laboratory is investigating the structural activity differences of these anthracycline agents. Tritton[2] and Rogers[3] have observed that Adriamycin still can exert cytotoxic effects when it is coupled to insoluble spheres or polymers which prevent free Adriamycin from entering the cell. These results indicate that cell-surface interaction may also play a role in the cytotoxic effects of Adriamycin. In our laboratory, experiments are under way to study the possible cell-surface effects that both Adriamycin and Menogaril may exert on parental and multidrug-resistant (MDR) CHO cells, obtained from Dr. V. Ling, Ontario Cancer Institute.

We are studying both amino-acid transport -- an active system, and membrane fluidity -- both of which reflect membrane integrity. Alteration in amino-acid transport will be examined using a rapid uptake technique, developed by Gazzola[4]. Changes in membrane fluidity before and after treatment with both anthracycline agents will be observed through changes in polarization of fluorescent probes, such as 1,6-diphenyl hexa-1,3,5 trieve (DPH) embedded in the hydrophobic region of the membranes.

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METALLOTHIONEIN GENE AMPLIFICATION AND REGULATION IN VIVO*

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In mice, metallothioneins are induced by a variety of factors, including heavy metals and hormones, and in some tissues are regulated developmentally. Control of expression is reflected in several qualitatively distinct changes in chromatin structure, which are associated with potential and actual rates of gene transcription[1,2]. We have shown that in vivo treatment of mice with high levels of cadmium results in a tissue-specific, two- to threefold increase in MT-1 gene dosage in mouse liver DNA in relation to both alfafetoprotein gene concentration and the bulk of DNA[3]. The extra gene copies persist for at least three months in the absence of subsequent doses of cadmium. Early (6 h) after induction, amplified MT-1 genes are relatively nuclease-resistant but, within three days, undergo a change in chromatin structure, which renders them nuclease sensitive. This change in chromatin structure is accompanied by an increase in the rate of transcription of MT-1 genes to a level approximately twofold higher than that maximally inducible in mouse liver with low MT-1 gene copy number[3]. While this increase in copy number is small in relation to amplification of other genes in cultured cells, some have argued that, in humans, low-level amplification (less than fivefold) may be biologically important in cellular resistance to chemical toxicity. Two mechanisms can be postulated to explain the appearance of amplified MT-1 genes in organs in situ after heavy metal treatment. First, *de novo* amplification of extra MT-1 genes might occur in most, or all, liver cells. Second, a subpopulation of cells with pre-existing high MT-1 gene copy number could be selected for preferential DNA replication. These possibilities are being explored by looking at variation in metallothionein expression and gene copy number in mouse liver cells in situ during morphological development and after cadmium treatment.

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METALLOTHIONEIN EXPRESSION AND RESISTANCE TO RADIATION AND CHEMOTHERAPEUTIC DRUG TREATMENT*

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The development of resistance to radiation or chemotherapy by malignant cells is a significant cause of failure of cancer therapy. Metallothioneins are a class of proteins that have been associated with resistance to killing by radiation and chemotherapeutic agents. It is hypothesized that metallothionein molecules act as sacrificial targets, sparing critical cellular macromolecules from damage by reactive cytotoxic agents. We have observed that chemotherapeutic agents and radiation, which are unable to induce metallothionein expression in cultured cells, can induce expression in mouse in an organ-specific pattern, and that pattern does not depend only upon the concentration of inducing agent present in each tissue[1,2] Therefore, metallothionein expression may be important in protecting normal patient tissues from damage by chemotherapeutic agents and radiation. On the other hand, expression in individual cancer cells may contribute to cellular drug resistance in tumors. We are studying the role of metallothionein as specifically as possible by transfecting mouse metallothionein genes into recipient mouse lymphoma cells, which are deficient in constitutive and inducible metallothionein expression. Transfected genes are under the control of the SV40 promoter, which allows expression in the absence of induction by toxic heavy metal treatment. In these cells, one can study as specifically as possible, the modulating effect of metallothionein expression on resistance to a variety of chemotherapeutic agents and radiation. These studies are done in the absence of the nonspecific effects of toxic metal induction including induction of cellular repair mechanisms, membrane protein changes, etc., which could play a role in mediating resistance.

This project is supported by a grant from the Victoria Hospital Research Development Fund.

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SOMATIC CELL GENETIC ANALYSIS OF METASTATIC CELLS*

A.F. CHAMBERS** and J.F. HARRIS†, *London, Ontario*

Cancer is characterized by phenotypic change, which results, for example, in tumor progression to drug resistance and metastatic ability. This change is based on the apparent phenotypic instability of tumors and on the development of cellular heterogeneity for a wide variety of properties. Some have proposed genetic and epigenetic mechanisms for tumor heterogeneity but the relative contributions of these mechanisms remain poorly understood.

We have proposed a dynamic heterogeneity model to explain the results obtained from tumor-cell-cloning experiments[1-6]. This model postulates that variant phenotypes with increased metastatic ability are generated and lost at measurable rates. However, these new phenotypes are not stable for individual cells. Populations of cells maintain a stable phenotype by a dynamic balance of newly arising and lost phenotypes. Rates of generation of metastatic cells may be calculated in murine fibrosarcoma[1,4-6], and melanoma[2] cell lines using Luria-Delbruck fluctuation analyses. We also observed loss of metastatic variants[4,5]. Numerically, the rates calculated (~1-5 x 10^{-6}) were consistent with rapid genetic processes such as gene amplification. A calculated rate, however, can only suggest mechanisms, and further work is required to confirm or refute this suggestion.

We have taken a similar approach to the study of tumor cell instability, analyzing the relationship between malignant transformation and instability for the generation of drug-resistant cells[7]. We used tsLA23-NRK cells, in which malignant transformation is under the control of a temperature-sensitive (ts) src oncogene. Cells were maintained in vitro as transformed (36°C) or as normal cells (39°C). Genetic instability was assessed by determining (a) the frequencies of methotrexate-resistant variants in the cell populations, and (b) the rates of generation of methotrexate resistant variants as determined by Luria-Delbruck fluctuation analyses. We observed no significant differences in either of these parameters of genetic instability, that could be attributed to transformation status[7]. These results, coupled with those from other groups, suggest that the inter-relationships between malignant transformation and genetic and epigenetic instability are complex, and that we have much to learn about the generation of phenotypic instability in tumor cells.

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* CS-150-2.

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THE CONTRIBUTION OF ONCOGENES TO TUMOR METASTASIS*

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Tumor metastasis is a major complication of cancer, hence understanding the molecular basis of tumor metastasis is of potential clinical importance. My laboratory is taking a number of related approaches toward these molecular mechanisms. Earlier, using genomic DNA transfection, we showed that metastatic properties could be transferred from metastatic murine and human tumor cells to non-metastatic recipient cells[1]. When these studies were extended to an examination of the contributions of various oncogenes to metastatic ability, we found that the *src* oncogene can induce such ability[2]. This study made use of a unique feature of the metastasis model which we developed in the naturally immune-deficient chick embryo[3-4] (reviewed in ref. 5), namely the ability to test temperature-sensitive mutants in vivo. We are using this assay and metastasis assays in synegeneic and athymic nude mice to assess the contribution of *ras* oncogenes to the metastatic process. Recently we reviewed the possible roles of different oncogenes in metastasis[6].

Earlier we reported that transfection of the T24 H-*ras* oncogene could increase metastatic ability of NIH 3T3 recipient cells[7]. Recently we showed that individual clones of *ras*-transformed NIH 3T3 cells are heterogeneous for metastatic ability, and that in these cells, there is a quantitative, direct relationship between levels of *ras*-encoded, p21 protein levels and metastatic ability[8]. These results suggest possible mechanisms for *ras*-induced increases in metastatic ability, namely, that one or more *ras*-induced genes may be responsible for *ras*-mediated increases in metastatic ability. Many functions are altered in *ras*-transformed cells, and we do not yet know whether all or only some of these changes are required for *ras*-induced increases in metastatic ability. At present, we are testing aspects of this hypothesis.

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* CS-150-3.

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STABILITY OF HUMAN MONOCLONAL ANTIBODY PRODUCTION IN MOUSE-HUMAN HYBRIDOMA CELLS*

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New developments in mouse monoclonal antibodies have facilitated their use as biological probes and potential therapeutic agents. However, the instability of human monoclonal antibody production by mouse-human hybridoma cells (and the lack of availability of a human fusion partner which does not secrete background immunoglobulins) limits the extension of this technology to human immunoglobulins. However, one mouse myeloma parent line (SHM-D33), in some clones at least, has proved as stable for human antibody production as mouse hybridoma cells are for mouse antibody[1]. Analysis of a panel of these hybridomas[2] has shown that: 1) there is a close correlation between loss of structural human antibody genes and loss of human antibody production; 2) there is considerable heterogeneity for human DNA content among antibody-positive cells; and 3) loss of antibody production is accompanied by large losses of human, but not mouse, DNA. Human DNA continued to be lost at a high rate thereafter. We are exploring genetic differences between clones of this type, both before and soon after loss of antibody production, to characterize the size and nature of DNA sequences lost at cessation of immunoglobulin production.

We have used hybridomas -- produced by fusion of SHM-D33 with human lymphocytes -- as good fusion partners. One of these is as efficient as the SHM-D33 fusion partner in producing human antibody-producing hybridomas. Now we can produce human antibody-secreting hybridomas at practical frequencies. In addition, we are exploring practical mechanisms to identify and isolate antibody-positive hybridoma cells from populations which tend rapidly to lose their ability to secrete human antibody.

The results of this work will be useful: In producing more efficient cellular sources of human monoclonal antibodies through the use of the teremyeloma hybridoma fusion partners which we have characterized; and by selecting good performers from the pool of resulting human antibody-producing hybridomas after fusion to extend productive life and increase antibody output. These studies will be extended to screen human antibody-producing hybridomas for cells which produce scientifically and clinically relevant antibodies encoded by human, rather than rodent, genes.

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DEVELOPMENT AND CHARACTERIZATION OF MONOCLONAL ANTIBODIES TO METASTATIC TUMOR CELLS*

J.F. HARRIS**, *London, Ontario*

We have proposed a "dynamic heterogeneity" model in which a subpopulation of specialized, highly metastatic cells are generated and lost during clonal expansion[1-4]. I have used this model to devise a screening procedure for the identification of monoclonal antibody (MAb) that recognizes a highly metastatic subpopulation of KHT fibrosarcoma cells. Embryonal carcinoma cells, which were recently derived from a liver metastasis[4], were used to immunize mice against a variety of developmental antigens, some of which would be related to metastasis. Using a sensitive immunochemical staining procedure, we isolated MAb 6E10, which stained preferentially the highly metastatic KHT35-L1[3] cells relative to the poorly metastatic KHTp cells. Quantitative absorption, binding and in situ immunochemical staining assays indicated that the MAb 6E10-defined epitopes are expressed differentially in KHT fibrosarcoma cell populations. Following cell harvesting from cultures at similar cell densities, the highly metastatic line KHT35-L1 expresses approximately 10-fold more antigen than weakly metastatic KHTp cells. Solution-phase competition and solid-phase, antigen-capture assays indicate that MAb 6E10 recognizes a restricted number of sulfated polysaccharides and glycosaminoglycans, related to heparin sulfate but not to chondroitin or keratan sulfates. There was a significant correlation ($p<0.05$) between the expression of MAb 6E10-defined antigen on the cells following trypsin treatment and the metastatic ability of the injected cells. In addition, there was a significant enhancement of the metastatic ability of KHT35-L1 cells when MAb 6E10 was incubated with the cells in vitro before injection.

These results suggest that increases in expression of sulfated polysaccharides, probably related to heparin sulfate proteoglycan determinants, are associated with metastatic cells in KHT fibrosarcoma. Future experiments will attempt to clarify the biology of these sulfated polysaccharides, and their functional involvement in metastasis.

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STRUCTURE AND FUNCTION OF PLASMA STEROID BINDING PROTEINS*

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Human blood contains two important, high-affinity, plasma-steroid binding proteins, which generally are known as corticosteroid binding globulin (CBG) and sex-hormone binding globulin (SHBG). Although steroid hormone transport is a major function of these proteins, they also appear to regulate the bioavailability of steroid hormones and may participate in the delivery of steroids to specific target cells[1].

It is known that patients with hematological malignancies frequently have unusually high plasma-CBG levels[2], and that women with breast and endometrial cancer have abnormalities in plasma SHBG levels and/or its steroid-binding properties[3,4]. Therefore, to define the structural and functional aspects of CBG and SHBG more precisely, we have used molecular biological techniques to clone and sequence cDNAs for these proteins, and thus have deduced the primary structures of both proteins[5,6]. This work has revealed that SHBG and CBG are structurally unrelated and do not resemble other steroid-binding proteins, including the steroid-receptor gene family[7]. Unexpectedly, however, we discovered that CBG is a member of the serine protease inhibitor (SERPIN) gene family[8], and thus our attention was directed to the possibility that the structural relationship between CBG and the SERPINs may be of functional importance.

The SHBG and CBG cDNAs have been used to isolate the human genes for this protein, and have enabled us to study the hormonal regulation of their expression in experimental animal models. Also phylogenetic comparisons of rat, rabbit and human CBG have revealed conserved regions which may have biological importance. Now site-directed mutagenesis will be used to produce variant proteins which should help to identify the structural and functional properties of these proteins at the molecular level. In various patient groups, several natural variants of SHBG and CBG have been identified and we will study their molecular characteristic in detail. It is anticipated that this work will help us understand more clearly the mechanisms by which steroid hormone enters target cells and will provide insight into the etiology and possible control of hormone-dependent cancers.

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RECOMBINANT INTERLEUKIN-2 (RIL-2) AND INDOMETHACIN: A NEW APPROACH TO CANCER IMMUNOTHERAPY*

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and D. BANERJEE‡‡, *London, Ontario*

During the development of transplanted and spontaneous tumors in mice, host NK cells are inactivated rapidly by NK suppressor cells, identified as tumor-infiltrating macrophages. This process is mediated by E-series prostaglandins (especially PGE_2), and NK activity can be restored in the presence of indomethacin in vivo and in vitro. Chronic indomethacin therapy via drinking water (a) reduces primary tumor growth, (b) is capable of preventing spontaneous lung metastases, (c) is associated with NK activity restoration, and (d) loss of NK suppressor ability of the tumor-infiltrating macrophages.

PGE_2 in vitro suppresses the activation of NK cells, T cell, and LAK cell development; the responsible mechanisms so far identified are: inhibition of IL-2 production by otherwise stimulated T cells; and down regulation of IL-2 receptor development.

Because chronic indomethacin therapy and IL-2 may be complimentary in producing adequate levels of LAK cells in vivo, we did further experiments using B6 mice injected intervenously with highly metastatic B16F10 melanoma cells. Without therapy, the mice developed profuse pulmonary micrometastases by day 5, macrometastases by day 10, and confluent metastases by day 21. Chronic indomethacin therapy via drinking water (14 µg/ml) started on day 0 or 5, or a single round of RIL-2 therapy (RIL-2 25,000 units q8h IP day 10 through 14) reduced the number of metastatic nodules by two-thirds when examined on day 21. A single round of RIL-2 therapy combined with either indomethacin schedule completely or nearly completely eradicated the lung metastases. Further experiments with chronic indomethacin therapy and either single or multiple rounds of RIL-2 therapy showed that both schedules totally or nearly totally eradicated the lung metastases at 21-25 days, but only multiple RIL-2 rounds gave long-term survival

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[*] PO-270.

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(>8 months). Subsequent experiments showed that intermittent indomethacin administration, given only at the [illegible] of RIL-2 administration, gave results inferior to continuous therapy, and were indistinguishable from RIL-2 therapy alone.

Based on our animal studies, we designed a clinical trial, in patients with advanced melanoma and renal cell carcinoma, to determine the toxicity and efficacy of continuous oral indomethacin and intermittent courses of RIL-2. Using a classical Phase II design, over a 3-year period, 14-25 patients with renal cancer and a similar number with melanoma will receive indomethacin 75-225 mg/day by mouth continuously and three 5-day (interspaced by 6-day rest periods) courses of continuous infusion IL-2, $3x10^6$ units/m^2 escalating to 4.5, then $6.0x10^6$ units/m^2 by the third course, if toxicity permits. Immunological parameters and indomethacin levels will be monitored. To date, nine patients have entered this study and toxicity has been predictable. It is too early to evaluate efficacy.

ADDITIONAL INVESTIGATIONS

Dr. L. Levin, Director of the London Regional Cancer Centre, reports on the following clinical research investigations:

MELANOMA AND RENAL-CELL CANCER

Dr. V. Bramwell is co-ordinating a study of the use of interleukin-2 and indomethacin for patients with advanced melanoma and renal-cell cancer. Dr. W. Mertens is working directly with Dr. Bramwell on this study. Funding comes from the NCI and NCIC grants.

SARCOMAS

Dr. V. Bramwell is the national co-ordinator/chairperson for the Canadian Sarcoma Group, which collaborates with the EORTC on clinical studies. A data base has been established for all sarcomas presenting to the London Centre since 1948. This group is partly funded by the NCIC.

AUTOLOGOUS BONE MARROW REINFUSION (TRANSPLANTATION)

Recent evidence suggests that high-dose chemotherapy with the support of autologous bone marrow reinfusion can produce prolonged disease-free survival in 20-25% of patients with diffuse, large-cell lymphoma or Hodgkin's disease refractory to standard chemotherapy and radiotherapy. Bone marrow harvests will be done by Dr. Anne Smith in the London Centre's operating suite. This program will enable the Centre to participate in clinical research protocols, which evaluate dose intensity in a variety of tumors.

LYMPHOMAS

Dr. J. Skillings is the study chairperson for an NCIC funded Phase II study of menogaril in "favorable-prognosis" lymphomas. A lymphoma data base provides information about prognostic factors and permits audit of treatment results in Hodgkin's disease and non-Hodgkin's lymphoma.

OVARIAN CANCER

Dr. L. Levin co-ordinates an in-house study of the combination of cisplatin/carboplatin and cyclophosphamide in ovarian cancer. We hope to undertake a collaborative study with the Hamilton Regional Cancer Centre to assess the use of high-dose carboplatinum and cyclophosphamide, in association with the biological response modifier GMCSF as a myeloprotective agent. Dr. Levin is co-principal investigator in the current NCI study.

ENDOMETRIAL CANCER

Dr. L. Levin is co-principal investigator in a study incorporating eight cancer centres in Ontario, Calgary and the North Central Cancer Treatment Group (including the Mayo Clinic); this examines the impact of whole abdominal irradiation and medroxyprogesterone acetate as adjuvant treatments for high-risk endometrial cancer. This study was developed and co-ordinated through the Ontario Clinical Oncology Group with support from the Upjohn Company of Canada.

PROSTATIC CANCER

The London Regional Cancer Centre is at the forefront of clinical research in brachytherapy for prostatic cancer. Under the direction of Drs. A. Porter, P. Corbett and J. Battista, the London Centre is the national co-ordinating centre for strontium studies in prostatic cancer, in collaboration with the Division of Nuclear Medicine of the Victoria Hospital.

BREAST CANCER

Of all the "diet-related" cancers, breast cancer has shown one of the strongest relationships to diet. D. Goettler and Dr. L. Levin are co-investigators studying the influence of dietary fat on hormone release in post-treatment breast cancer. They are working in collaboration with the Department of Biochemistry, University of Western Ontario, and the Gastrointestinal Centre at Genessee Hospital in Rochester, N.Y.

LUNG CANCER

D. Goettler and Dr. L. Levin, in collaboration with the Departments of Surgery and Pathology, Victoria Hospital, are investigating the relationship between Vitamin A, cell differentiation and proliferation rates in lung cancer.

BRAIN TUMOR STUDIES

Dr. J.G. Cairncross reports that the treatment of adult malignant glioma remains the research focus of the neuro-oncology group at the London Centre. Clinical research interests include Phase II and III trials assessing chemotherapeutic approaches to the treatment of newly diagnosed and recurrent malignant glioma in adults. We plan further clinical and laboratory studies of malignant oligodendroglioma, which recent observations suggest is a uniquely chemosensitive glial tumor. An area of special interest is methods to assess response to treatment. Studies are underway of cognitive and neuroendocrine function in successfully treated brain tumors.

Ottawa Regional Cancer Centre

SIGNAL TRANSDUCTION PATHWAYS RESPONSIBLE FOR INDUCTION OF GENE EXPRESSION EARLY FOLLOWING ACTIVATION OF PROTEIN KINASE C*

H.C. BIRNBOIM** and R.G. LITEPLO†, *Ottawa, Ontario*

A number of cellular events occur shortly after stimulation of quiescent cells with phorbol myristate acetate (PMA) -- a tumor promoter and activator of protein kinase C (PKC). One of these is the induction of expression of several genes, including proto-oncogenes and other genes of known and unknown function. Our work has sought to identify some of the biochemical steps (signal transduction pathways) that are required for gene induction between the initial activation of PKC by PMA and the late step of binding of a transacting factor (protein) to defined sites on the DNA. For these studies we have examined the induction of two proto-oncogenes (*c-fos* and *c-myc*) and a third gene of unknown function (EGR, early-growth-response gene). A pharmacological approach was used: A hypothesis was developed which led to the testing of agents not previously known to affect the induction of these genes by PMA. We tested a non-steroidal anti-inflammatory agent, indomethacin (INDO), because of the possibility that prostaglandins were part of the signal transduction pathway. INDO had a marked effect on induction of these three genes, but only at concentrations which were much higher than that usually needed to inhibit prostaglandin synthetase. Total RNA was prepared from treated quiescent Balb/c 3T3 A31 cells by a newly developed procedure[1]. Levels of mRNA for *c-fos*, *c-myc* and EGR were measured by Northern analysis at different times after PMA treatment in the presence or absence of INDO. Soon after PMA addition, INDO strongly inhibited the increase in mRNA levels of all three genes. However, for *c-fos* and EGR in the continuous presence of INDO, the levels of mRNA rose at later times to levels as high or higher than those reached earlier in the absence of INDO.

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* CS-104-2.

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In other words, INDO delayed induction of these mRNAs by about one hour, but did not actually inhibit them. In *c-myc*, we observed no delayed rise in mRNA in the presence of INDO during the three hours after PMA was added. These results indicate that INDO can disturb the signal transduction process, although the specific site of its action remains to be elucidated. At these concentration, INDO has been reported to inhibit protein kinases. This drug may help to understand better the details of the signal transduction processes involved in the induction of genes.

This project is supported by grants from the Medical Research Council of Canada, and the National Cancer Institute of Canada.

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MECHANISM OF OXYGEN-RADICAL DAMAGE TO CELLULAR DNA AND ITS ROLE IN TUMOR PROMOTION AND TUMOR PROGRESSION*

H.C. BIRNBOIM**, *Ottawa, Ontario*

We have continued our study into the mechanism by which oxyradicals, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), cause strand breaks in the DNA of intact cells. These oxyradicals are produced by phagocytic cells such as neutrophils which are present in inflammatory extracts and in solid tumors. We have postulated that such oxyradicals contribute to the "promotion" and "progression" stages of cancer by activating a metabolic pathway resulting in DNA strand breaks; in turn, strand breaks can lead to genomic alterations such as translocations, rearrangements and amplifications. Such genomic alterations may activate a second oncogene in an early tumor cell if one oncogene already has been activated as a result of exposure to a carcinogen -- causing it to progress to a more malignant phenotype. Alternatively, these genomic alterations may inactivate tumor-suppressor genes such as the product of the retinoblastoma locus. Our model may help to explain why: i) various inflammatory conditions such as ulcerative colitis can predispose to malignancy; and ii) the nature of "spontaneous" events leading to tumors in individuals bearing one defective retinoblastoma locus.

It is widely assumed, based upon indirect evidence with oxyradicals and upon studies using ionizing radiation, that O_2^- and H_2O_2 cause strand breaks in DNA via generation of hydroxyl radical ($HO\cdot$) -- a highly reactive oxyradical species. While this likely is true in intact cells exposed to ionizing radiation and pure DNA exposed to oxyradicals in solution, we do not believe this is the mechanism by which O_2^- at the external surface of a cell causes strand breaks in nuclear DNA. In our experiments, we stimulate human neutrophils with a tumor promoter (PMA). Then the cells are monitored for the amount of O_2^-, which they generate, as well as for the number of breaks introduced into their DNA. H_2O_2, which is derived from O_2^-, is eliminated by addition of catalase. O_2^- is shown to be responsible for the breaks: if O_2^- is removed using a O_2^--specific enzyme (superoxide dismutase) or chemicals which react with O_2^-, one can prevent strand breakage. Depletion of intracellular Ca^{++} and Mg^{++} with ionophores and chelators also prevents strand breakage. Conversely, strand breakage can be enhanced with: i) sodium orthovanadate --

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* CS-104-3.

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a phosphate analogue which can inhibit cellular phosphatases; and ii) o-phenanthroline -- a lipophilic chelator. Involvement of an Fe(III)-containing site at the cell surface is suggested by the observation that Desferal, a strong iron-binding compound, partially blocks strand breakage. Although we do not understand the mechanism, the evidence that we have adduced strongly supports the notion that a metabolic process, triggered by O_2^-, is important for strand breakage. If a similar metabolic pathway exists in other cells, our model may help to explain the generation of genomic alterations frequently observed in tumor cells.

This project is supported by a grant from the Medical Research Council of Canada.

ALTERATIONS IN METHIONINE METABOLISM ASSOCIATED WITH TUMOR PROGRESSION*

R.G. LITEPLO**, *Ottawa, Ontario*

Neoplasms are believed to arise from the oncogenic transformation of single cells. In time, however, such cells tend to become phenotypically and genotypically heterogenous and increasingly more malignant. There is a great deal of interest in identifying those cellular and/or biochemical alterations which are associated with or contribute to the "malignant phenotype". Recently, our laboratory has begun to examine how alterations in methionine metabolism and S-adenosylmethionine-dependent transmethylating activities may contribute to the progression of human tumors from relatively benign to highly malignant and autonomous states.

Normal cells (as well as some human tumor cell lines) can grow in vitro in culture medium devoid of exogenous methionine but containing its immediate precursor -- homocysteine. Such cells are termed "methionine-independent". In contrast, many human tumor cell lines (and most transformed rodent cells) cannot grow in such methionine-free, homocysteine-supplemented culture medium; these have been termed "methionine-dependent". We have found that a series of highly metastatic, variant cell lines, which had been derived from a poorly metastatic (and methionine-independent) human tumor line, exhibit a "methionine-dependent phenotype". In addition, a large proportion of anchorage-independent cells obtained from two methionine-independent human tumor cell lines exhibit this "methionine-dependent phenotype". These observations suggest that alterations in methionine metabolism (possibly arising from changes in certain S-adenosylmethionine-dependent transmethylating activities) may play an important role in the evolution of human tumors towards a highly autonomous and malignant state.

This project was supported by a grant from the National Cancer Institute of Canada.

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*CS-108-2.

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MECHANISMS ASSOCIATED WITH THE ACQUISITION OF AUTONOMOUS GROWTH CHARACTERISTICS IN NEOPLASTIC CELLS*

R.G. LITEPLO** and H.C. BIRNBOIM†
Ottawa, Ontario

An important but poorly understood aspect of cancer biology is the cellular processes that are responsible for the generation of heterogeneity within a tumor-cell population and the progression of a developing tumor from a relatively benign to a highly autonomous and malignant state. Previous studies from our laboratory had established a new in vivo model system to examine these processes. The systemic administration of the tumor promoter, phorbol myristate acetate (PMA), to experimental animals, previously inoculated with a methylcholanthrene-induced mouse sarcoma line called MC1A, caused a large proportion of the tumor cells to acquire an altered immunological phenotype.

To examine the mechanism(s) responsible for this phenotypic alteration, the MC1A tumor line was adapted to grow in tissue culture and individual clones isolated. The tissue-culture-adapted MC1A cells (MC1AG2) exhibit a marked increase (greater than 30-fold) in their ability to grow in an anchorage-independent fashion, compared to MC1A cells freshly isolated from tumors. These anchorage-independent cells may either pre-exist in the tumor or arise at high frequency once they are placed into tissue culture. At the present time, we are examining the effects of in vivo and in vitro PMA treatment, the role of host cells, and the effect of oxygen radicals on the generation of these anchorage-independent MC1A cells.

This project is supported by a grant from the Cancer Research Society Inc.

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* CS-108-3.

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INTERLEUKIN NETWORKS IN B-CELL DIFFERENTIATION AND NEOPLASIA*

R.G. HAWLEY**, *Ottawa, Ontario*

B-cell lymphopoiesis is a complex developmental process mediated by soluble glycoprotein factors, termed interleukins. A major obstacle in elucidating the molecular signal transduction events elicited by interleukins is the difficulty in obtaining sufficient quantities of homogeneous, normal-responder, B-cell populations. These difficulties can be circumvented by deriving interleukin-responsive B-cell lines.

We are employing a novel strategy to generate B-cell lines, which involves retroviral vectors containing lymphokines and/or oncogenes to immortalize primary murine B-cells and B-cell progenitors. To restrict the expression of retrovirally-transduced genes to lymphoid cells, the genes of interest have been placed under the transcriptional control of immunoglobulin gene-enhancers and promoters. We postulate that the autologous synergistic action of different lymphokine-oncogene combinations will permit the isolation of B-cell lines, which vary in their differentiation states and interleukin requirements. The interleukin-dependent B-cell lines so generated will allow identification of the interleukin-responsive genes which are critical elements in B-cell growth control. Subsequent characterization of interleukin-independent variants should provide insight into the mechanisms involved in the autonomous growth of B-cell neoplasms.

This project was supported by a grant from the National Cancer Institute of Canada.

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* CS-110.

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EXPRESSION OF PLATELET DERIVED GROWTH FACTOR GENE IN THE BACULOVIRUS*

D.M. LOGAN** and C-Y. KANG†, *Ottawa, Ontario*

The baculovirus -- *Autographa californica nucleopolyhedrosis* virus (AcNPV) is an invertebrate virus. When the baculovirus carrying a foreign gene infects the pural ovarian cells of the moth *Spodoptera frugeperida*, large quantities of a recombinant product with appropriate post-translational modifications including glycosylation and phosphorylation is synthesized and secreted. The conventional method of expression using prokaryotic cells such as *Eschericha coli (E.coli)* does not yield gene products which are properly modified post-translation; this may affect the biological activity of the protein product[1].

The aim of this study is to insert the platelet derived growth factor gene (PDGF) into the PACYM1 vector to permit expression of the protein product in the baculovirus system, and to evaluate the biologic activity of a properly post-translationally modified PDGF product. Before the insertion of the PDGF gene into PACYM1, both the upstream and downstream DNA sequences are being modified using double-stranded, cross-over "linkers" to remove DNA sequences which would interfere with the expression of the protein product.

During the past year, the upstream sequence of the PDGF gene has been modified. Currently the downstream sequence of the PDGF gene is being modified. During the next year, the modified gene will be transfected into the baculovirus. Then the secreted product will be isolated and evaluated for its biologic activity.

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* CLS-001.

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KAPOSI'S SARCOMA -- AN IN VITRO STUDY*

D.M. LOGAN**, C.A. IZAGUIRRE†, L.B. HUEBSCH†† and C-Y KANG‡
Ottawa, Ontario

Epidemic Kaposi's sarcoma (EKS) develops in up to 30% of patients with the acquired immunodeficiency syndrome (AIDS), particularly in male homosexuals. EKS lesions may appear in skin, mucosal membranes, lymph nodes, GI tract and lung. EKS produces significant patient morbidity by ulceration, obstruction or lymphedema and current therapies, if effective, induce only temporary remissions[1,2].

Development of effective therapy has been hampered by the lack of an in vitro model, such as a cell line, to determine the biologic characteristics of EKS, the agent(s) responsible for transformation to EKS, and the evaluation of potential therapies.

The aims of this research project are:

1. To establish EKS cell cultures to use as an in vitro model for EKS.
2. To test the hypothesis that EKS is the result of activation of an unidentified growth-factor gene, either by antibodies against HIV and/or a virus other than HIV.
3. To develop effective therapies for EKS.

The first goal has been achieved during the past year. Three EKS cell cultures have been established from three different patient EKS biopsies. Initial studies have demonstrated that EKS cell cultures are composed of polygonal cells which form whorls and lack contact inhibition; propagate slowly; originate from nonvascular endothelial cells (based on immunohistological evaluation) and do not contain HIV (based on Southern blot analysis with an HIV-specific probe). Furthermore, we have determined that the EKS cells are endothelial-cell, growth-factor dependent. EKS cell growth is enhanced by the addition of supernatant from HIV infected HUt78 cells (lymphocyte line) and to a lesser degree by the addition of supernatant from EKS cells. Recently, Gallo[3] also confirmed the latter finding -- growth enhancement.

During the next year, we will undertake investigations to identify the growth factor(s). Once this second goal has been achieved, investigations will pursue the third goal -- of defining effective therapies.

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* CLS-001-1.

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† Associate Professor of Medicine, University of Ottawa.

†† Hematologist, Ottawa General Hospital; and Assistant Professor of Medicine, University of Ottawa.

‡ Chairman and Professor, Department of Microbiology and Immunology, University of Ottawa.

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ADDITIONAL INVESTIGATIONS

Dr. W.K. Evans, Director of the Ottawa Regional Cancer Centre, reports on the following clinical research investigations:

In 1987, 384 patients were entered on clinical trials at the Ottawa Regional Cancer Centre, and accrual in 1988 has remained active. Presently, 85 active clinical protocols are accruing patients. The Centre is participating in NCIC, NSABP, pharmaceutical company, and local studies, which include adjuvant chemotherapy of breast cancer, osteogenic sarcoma, colorectal carcinoma, and non-small cell lung cancer. Studies combining chemotherapy with radiotherapy are underway in bladder carcinoma, glioblastomas, primary central-nervous-system lymphoma, advanced head and neck carcinoma, cervix carcinoma, non-small cell lung cancer and small cell lung cancer. Studies of chemotherapy in advanced or metastatic disease are underway in breast cancer, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, hairy-cell leukemia, soft tissue sarcomas, Kaposi's sarcoma, colon carcinoma, hepatocellular carcinoma, ovarian carcinoma, superficial bladder tumors, renal cell carcinoma, prostate carcinoma, testicular carcinoma, glioblastomas, brain carcinoma, and small cell lung cancer. Also a number of Phase I studies, pharmacology studies, and a variety of tumor biology studies are underway. Radiotherapy studies are underway in breast cancer and non-small cell lung cancer. The notable high point in the clinical research was our demonstration that we had a high complete remission rate when we combined intra-arterial cisplatin with radiation in localized bladder cancer.

INTERSTITIAL HYPERTHERMIA AND BRACHYTHERAPY PROBE

Investigators: G.P. Raaphorts, L.H. Gerig, J. Cygler, A. Ginsburg and S. Kashyap

In collaboration with Macom Associates, a spiral interstitial microwave hyperthermia probe is being developed to incorporate iridium for iridium-192 brachytherapy. Two approaches are being tested: the construction of the probe with iridium wire which subsequently is activated by neutron activation; and the construction of a probe with an area which will accept already activated iridium-192 wire. Temperature mapping of the spiral probe performance in tissue equivalent phantom material is ongoing.

MEASUREMENT OF PORCINE TISSUE BLOOD FLOW AND pH DURING HYPERTHERMIA

Investigators: L.H. Gerig, A. Ginsburg, G.P. Raaphorst, C.E. Danjoux, G. Forester and P. Watson

Failure to control local disease is a major cause of human morbidity and mortality. Hyperthermia combined with chemotherapy or radiation is proving to be of clinical benefit. However, until predictions of temperature distribution (treatment planning) become accurate, hyperthermia will never realize its full potential. A principal factor in determining the temperature profiles in tissue is blood flow, which is known to be a function of temperature. The dependence varies from tissue to tissue, malignant to normal, and has not been well quantified in any large animal system. As well, tissue microvasculature itself may be a target of hyperthermia.

This project will quantify the effect of hyperthermia on normal muscle and organ blood flow in a porcine system. The data will be used to determine blood flow in our human clinical trials and to develop predictive planning models for clinical hyperthermia.

A specific aim is to compare three different methods of measurement of blood perfusion and use this information to perfect and calibrate the thermal washout technique. The three methods are: the venous outflow, which uses electromagnetic detection; the trapping method using radiolabelled microspheres; and thermal washout.

All animal work for this project is being carried out at the National Research Council of Canada, Biomedical Engineering Laboratories, Ottawa.

HYPERTHERMIA AND RADIATION: STUDIES ON INHIBITION OF CELLULAR REPAIR AND THERMORADIOSENSITIZATION IN HUMAN NORMAL AND TUMOR CELLS

Investigators: G.P. Raaphorst, M. Feeley, V.F. Da Silva, C.E. Danjoux and L.H. Gerig

Some cancers respond poorly to radiation and chemotherapeutic agents. One explanation for this is that these cells and tissues can repair the damage caused by such agents. This research project will evaluate human derived tumor cells such as glioma, melanoma and squamous-cell carcinoma with respect to their radiosensitivity in culture. We will attempt to correlate radiation response with ability to repair radiation damage. Hyperthermia is used to cause radiosensitization and inhibit repair of radiation damage. To date three glioma and two melanoma cell lines have been tested. The results show that hyperthermia causes greater cell killing in glioma cells than in normal fibroblast cells especially at lower hyperthermia temperatures; also, hyperthermia can inhibit the accumulation of sublethal radiation damage.

HIGH-DOSE-RATE RADIATION IN HUMAN CELLS

Investigators: J. Cygler, M. Feeley, G.P. Raaphorst, N. Klassen and C.K. Ross

We are studying response of human glioma cells to high-dose rates of radiation under oxic and anoxic conditions. NRC research linear accelerator is used as a source of high-dose-rate electron pulses. To date, we have determined the plating efficiency of the cells on glass and determined survival curves of the cells plated on glass and on plastic, irradiated with 60_{Co}. We have collected glassware, gases and other equipment to be used in the project.

DEVELOPMENT OF A COMPUTERIZED MICROTHERMACOUPLE THERMOMETRY SYSTEM

Investigators: L.H. Gerig, G.P. Raaphorst, A. Ginsburg and C.E. Danjoux

Thermometry plays a major role in the application of clinical hyperthermia. To assess the contribution of hyperthermia when combined with other treatments one must be able to measure the thermal dose delivered to the tissues. With the present technology the most reliable system for such measurement is the interstitial microprobe. The Ottawa Regional Cancer Centre has developed an interstitial microthermocouple probe containing up to 12 microthermocouples in a single probe, which can be fitted into a 19-gauge catheter. This microthermocouple probe is interrogated by a Keithley data acquisition system and controlled by a personal computer. A software program has been developed in Asyst for clinical temperature measurement and to control, to a limited extent, a microwave generator. We are doing more work to develop this system, e.g. the probes are being evaluated for their temperature reporting accuracy in steep thermal gradients.

A STUDY OF p31 HIGH-ENERGY METABOLITES IN RAT GLIOMA CELLS IN VITRO AND IN RAT BRAIN TUMORS USING NMR

Investigators: G.P. Raaphorst, D. Wilkins, R. Kroeker, I. Smith and J. Saunders

The literature indicates that the stress caused by therapeutic agents can cause changes in the high-energy phosphorous metabolites within cancer cells. This study will investigate the p^{31} spectroscopy of rat glioma cells in vitro and in vivo. To date, experimentation in a perfusion apparatus with the rat 9L cell line in vitro shows a low level of PCR and high levels of ATP. We are constructing a special probe to evaluate the p^{31} metabolites in a brain tumor resulting from these cells implanted in the brain of Fisher 444 rats. Both cells in vitro and in the tumor will be evaluated for responses to hyperthermia, radiation chemotherapeutic agents and combinations of these.

This project is being done in the laboratory of Dr. I. Smith, in collaboration with the National Research Council of Canada.

A STUDY OF BREMSSTRAHLUNG FROM HIGH-ENERGY LINEAR ACCELERATORS

Investigators: D.W.O. Rogers, G.P. Raaphorst, B.A. Faddegon and C.K. Ross

Radiation with high-energy photon beams depends on *bremsstrahlung*, derived from high-energy accelerated electrons colliding with a target. The energy spectrum and the distribution of such photons depend on the energy of the electron beam, the target material, target thickness and various other factors. Using the 35 MeV accelerator at the National Research Council of Canada, we are studying *bremsstrahlung* derived from an accelerated electron beam using different targets and different electron energies. The detector has been characterized and beam measurements are being made. Further energy calibration is still ongoing. These data will be valuable for modelling studies of various electron energies and their output configurations; also they are germane to radiotherapy and treatment planning of radiation beams.

This project is being done in collaboration with the National Research Council of Canada, in the laboratories of the Radiation Standards Group.

EVALUATION OF THERAPLAN ELECTRON BEAM ALGORITHM

Investigators: J. Cygler and J. Ross

Performance of Theraplan pencil-beam algorithm was compared with measurements done in anthropomorphic phantom. Head, neck and chest wall were irradiated with Therac 20 electron beams. We found big discrepancies (up to 40%) for the measured and calculated dose in lungs. Because we could not explain such a discrepancy in terms of assumptions inherent in the equation employed in Theraplan, we discovered an error in the software. We are preparing a paper to describe the results of this work. A practical result of this project has been the collaboration with the Atomic Energy of Canada Limited and their financial support for future research projects related to treatment planning.

STUDY OF LONIDAMINE AS A RADIOSENSITIZER, THERMOSENSITIZER AND CHEMOSENSITIZER OF RODENT AND HUMAN CELLS IN CULTURE

Investigators: G.P. Raaphorst, C.E. Danjoux, J. Maroun, M. Feeley and L. Martin

Lonidamine is a compound which has been used as contraceptive agent, specifically a spermaticide. Recent evidence indicates that lonidamine also may have therapeutic effectiveness in cancer. These studies will test the effect of lonidamine on rodent and human cells. Also, lonidamine will be combined with radiation to determine whether it acts as a radiation sensitizer and whether it can inhibit the repair of radiation damage. In addition, lonidamine is being evaluated as a thermal sensitizer and a sensitizer when combined with various other chemotherapeutic agents. Already we have completed studies on lonidamine combined with radiation on various human and rodent cell lines and shown only inhibition of radiation damage repair in one rodent cell line but not in human cell lines. Lonidamine caused thermal sensitization especially at low pH. This agent is being tested further for its usefulness in clinical therapy.

SUPPRESSION OF MOTION ARTIFACTS IN MRI

Investigator: R. Kroeker

Over the past few years, the quality of magnetic resonance (MR) images has been substantially enhanced by hardware improvements. However, because of relatively long imaging times, motion commonly limits image quality. Specifically, motion of subcutaneous fat and vascular pulsations generate ghost artifacts which propagate along the phase-encoding axis. These artifacts degrade image quality in several regions, including the chest, abdomen, pelvis and spine.

We have developed a technique to suppress these artifacts. Signals from tissues responsible for the artifacts are eliminated by radiofrequency pulses, specifically optimized for high selectivity; these saturate proton magnetization in one or more independently defined slabs of tissue. This also suppresses ghost artifacts from pulsatile flow in the heart and blood vessels, as well as respiratory motion.

THERMOCHEMOSENSITIZATION ON HUMAN RESISTANT TUMOR-CELL LINES

Investigators: V. Da Silva, M. Feeley and G.P. Raaphorst

Hyperthermia plays a major role in chemosensitization. Our studies will evaluate the effect of hyperthermia on several chemotherapeutic agents tested in human resistant tumor cell lines. We have shown that the effectiveness of several chemotherapeutic agents such as cis-platinum, BCNU, AZQ and SHM can be increased in human glioma cell lines by the application of hyperthermia. In addition, we are doing studies with a BCNU-resistant variant to determine whether hyperthermia can overcome such resistance. The results indicate that thermosensitization can also be achieved in cell lines resistant to BCNU. This strategy also may be applied to reduce resistance to other chemotherapeutic agents. We are testing different hyperthermia temperatures and times to determine maximum drug enhancement.

STUDY OF RADIOSENSITIVITY OF LYMPHOCYTE AND LYMPHOBLAST CELLS DERIVED FROM PATIENTS UNDERGOING CANCER THERAPY

Investigators: N. Gentner, D. Morrison, C.E. Danjoux and Associates, G.P. Raaphorst, J. Cygler and M. Feeley

One concept in radiation therapy is that, in general, the doses delivered to patients are limited by the response of a subpopulation who are more sensitive than the mean, or of another subpopulation who may be more resistant. In general, observation of normal tissue responses can set the upper limit for radiotherapy doses in all patients. To determine whether such heterogeneity exists in the human population, we are studying the radiation response of lymphocytes and lymphoblasts derived from patients at the Ottawa Regional Cancer Centre. These studies are being done at Atomic Energy of Canada Ltd. in collaboration with N. Gentner and D. Morrison, who have perfected the technique for such tests. With these data, we hope to determine if a heterogeneity exists in radiation response, to predetermine which patients are being treated to their optimum dose and which may be receiving more than optimal radiation.

CLINICAL HYPERTHERMIA OF MALIGNANT DISEASE

Investigators: C.E. Danjoux, L.H. Gerig, G.P. Raaphorst, S. Grimes and A. Ginsburg

Many papers in the literature indicate that hyperthermia can play a major role in the treatment of human cancer, especially when combined with radiation or chemotherapy. At the Ottawa Regional Cancer Centre, we are investigating a combination of microwave hyperthermia combined with radiation. To date, 20 patients have been treated in this manner. Radiation is applied using teletherapy or brachytherapy, and hyperthermia using an external 2450 MHz microwave applicator. The results, which are encouraging, suggest that we need to develop or acquire a system for deeper heating.

Thunder Bay Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. J.F. Kotalik, Director of the Thunder Bay Regional Cancer Centre, reports on the following clinical research investigations:

In the recent past, the medical oncology program in Thunder Bay has suffered from a shortage of personnel, and hence our priority has been delivery of service to the community. In the last six months, we have corrected deficiencies in our complement of physicians. We now have a more complete staff than ever before: two full-time medical oncologists and three radiation oncologists. We are in the process of establishing a more active clinical trials program.

In previous years, our chief activity has been participation in established collaborative programs, particularly the National Cancer Institute of Canada (NCIC). We have contributed patients to a number of NCIC trials, exploring therapeutic options in common malignancies; whenever possible, we use other trials which examine less common diseases, but our accrual is limited by the small patient numbers. Also we participate in two trials of the Ontario Clinical Oncology Group (OCOG), and in several other intergroup trials.

In the past, Thunder Bay Regional Cancer Centre has been affiliated with the North Central Cancer Treatment Group (NCCTG) as a satellite of the Duluth Clinic in Minnesota, and did enter a significant number of patients to this group's clinical trials program. With the loss of a medical oncologist in mid-1987, we suspended our participation in NCCTG trials. We have just submitted an application for reactivation of our connection with this group, initially as before through the Duluth Clinic. If this link is reestablished, we will have access to a large number of studies applicable to many of our patients. Already, in preparation for this, staff from the Clinical Trials Office have visited Duluth and Rochester, Minnesota.

The small patient population of Thunder Bay does not permit us to undertake autonomous trials in the management of malignant disease, but we expect to become more active in co-operative programs including, but not limited to, the above. The addition of a clinical psychologist to our staff should permit us to investigate the areas of symptom control and psychosocial impact of malignant disease.

To support this increased activity, we have expanded our clinical trials office and added a data manager and a nurse manager with previous experience in this area.

Available clinical trials in Thunder Bay can be applied only to a small proportion of the patients we treat. We hope to expand our program so as to permit us to manage a much larger fraction of our patients according to the protocol of prospective investigational trials.

BREAST CANCER

Accrual has been limited to the OCOG I trial that is examining the role of breast radiotherapy after segmental mastectomy in patients with node-negative disease because it has not been well received in this community. We have participated more actively in the NCIC's MA4 trial of adjuvant chemo- and hormonal therapies in patients with Stage II, hormone-receptor-positive disease.

LUNG CANCER

We have participated actively in NCIC BR6 that is examining optimal timing of thoracic irradiation in limited-stage, small-cell, anaplastic lung cancer. Patients with extensive small-cell disease are being considered for a pilot trial of chemotherapy co-ordinated by the Northeastern Ontario Oncology Program in Sudbury. Patients receiving irradiation for inoperable or recurrent non-small-cell bronchogenic carcinoma are being considered for a trial examining the use of lonidamine as a radiosensitizer.

COLON CANCER

There is available only one adjuvant trial. Patients with colon carcinoma resected for cure but with adverse prognostic factors are considered for the NCIC CO3 trial, which examines the role of adjuvant chemotherapy in this situation. NCIC CO4 trial that examines similar chemotherapy in addition to pelvic irradiation in patients with poor-risk rectal carcinoma, has been approved by our ethics committee but is not yet open for accrual.

LYMPHOMAS

Patients with advanced Hodgkin's disease are treated according to NCIC HD4 trial. Also available is a trial for the management of intracranial lymphoma.

MISCELLANEOUS

Other clinical trials availabe in Thunder Bay include NCIC HL1 (management of hairy-cell leukemia), ME5 (malignant melanoma), and BL3 (bladder carcinoma). NCCTG trials examining therapy of colon, lung, pancreatic, brain cancer, lymphoma and melanoma, have been approved again by our ethics committee, but we cannot start accrual again until (and if) we receive reaccreditation by the NCCTG.

Toronto-Bayview Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. R.D.T. Jenkin, Director of the Toronto-Bayview Regional Cancer Centre, reports on the following clinical investigations:

A PROSPECTIVE RANDOMIZED STUDY OF TAMOXIFEN COMPARED TO TAMOXIFEN PLUS SIX MONTHS OF CMF IN POSTMENOPAUSAL WOMEN WITH AUXILLARY NODE-POSITIVE BREAST CANCER

Investigators: K.I. Pritchard, S. Fine, and A.H.G. Paterson

A co-operative group from Toronto and Edmonton, including the authors listed above and a number of other investigators, undertook a prospective randomized study of postmenopausal, axillary-lymph-node-positive women who received either tamoxifen 30 mg daily for two years or tamoxifen 30 mg daily for two years plus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) every three weeks for eight treatments -- about six months. The original sample size was 300 patients. Initial funding was obtained from the Medical Research Council of Canada. Within a few months of the trial's opening in 1984, the Clinical Trials Group of the National Cancer Institute of Canada (NCIC) joined the core investigators for a multi-centre, cross-Canada study with data co-ordination by the Clinical Trials Group office. Dr. Pritchard is study chairman, Drs. Paterson and Fine are members with others working through the NCIC Clinical Trials Group Protocol Committee. The Medical Research Council of Canada continues to provide core funding.

Because this group of patients have extremely favourable survival rates, the group decided to increase the sample size to 500 patients to improve the power of the study. Over 400 patients have been randomized but no formal analysis will be done until full accrual has been completed. The NCIC Clinical Trials Group, under the guidance of Drs. Paterson and Pritchard, will provide quality control and toxicity monitoring.

A multi-centre Toronto-Edmonton study, funded by the Medical Research Council of Canada, has been expanded into a nation-wide study with the NCIC Clinical Trials Group. Projected sample size has been increased from 300 to 500 and the combined investigators have nearly reached that goal. Study results should be available in 1989.

ESTROGEN AND PROGESTERONE RECEPTORS – HUMAN BREAST TUMORS

Investigator: D.J.A. Sutherland

The receptor laboratory continues to collect specimens from breast tumor biopsies done throughout the Metropolitan Toronto region. The file on these patients now includes information on more than 20,000 specimens.

Preliminary analysis of these data has confirmed many previously demonstrated relationships including the relative stability of receptors in serial specimens, the general increase in receptor level with age, and the tendency for estrogen and progesterone receptors to correlate positively in individual specimens.

During the coming year, we will attempt an in depth look at the recurrence and survival patterns in relationship to receptor status in node-negative women.

STEREOTACTIC RADIOSURGERY

Investigators: R.D.T. Jenkin, C. Catton, P. O'Brien, R. Barnett, H.B. Michaels, B. Gillies, R. McVittie, S. Chippett, G. Scott, G. Peterson and K. Krohmer

The Toronto-Bayview Regional Cancer Centre (T-BRCC) employs the McGill technique for stereotactic radiosurgery, primarily to treat arteriovenous malformations (AVMs) in the brain. We have modified a commercial 6 MeV electron linear accelerator to deliver a 1 cm diameter photon beam and to provide synchronous gantry and couch motion. Diagnostic and radiotherapy planning is done on an IBM-compatible, personal computer (Intel 386-20), which has been configured with peripherals to use several digital image modalities including CT, MRI and DSA. The small-diameter photon beam is not limited to AVMs and may be useful for other sites, e.g. brain tumors, involving small (less than 4 cm diameter) target volumes. However, precision radiotherapy of these other sites will require new techniques for target localization, improvement of existing dosimetry methods, and new planning software that accurately can model dose measurements from this type of field. The last is a particularly challenging problem because most dosimetry involves interfaces and penumbral regions where charged particle equilibrium is non-existent.

Recently, T-BRCC developed a digital film densitometry system that is well suited to make dose measurements for stereotactic radiosurgery. This system offers good (<0.3 mm typical) spatial resolution and can provide dose profiles along arbitrary directions. New developments (convolution techniques) in photon beam-dose calculations permit us to handle situations where charged particle equilibrium is non-existent. However, at present these calculations are non-interactive and require many hours of Monte Carlo simulation. The T-BRCC Department of Physics has telephone access to a computing facility, which can be used for this type of development.

DOSIMETRY OF RADIOLABELLED MONOCLONAL ANTIBODIES FOR TREATMENT OF MALIGNANCY

Investigators: H.B. Michaels and R. Reed

This project focusses on identification and characterization of immediate, medical-physics considerations arising from a collaborative pilot study, with Toronto-Bayview Regional Cancer Centre's medical oncologists, on the use of radiolabelled monoclonal antibodies in advanced ovarian carcinoma. These considerations include practical and technological aspects of the treatment, including radiation protection, dosimetry and treatment planning.

Patients receive a tracer dose, followed by a therapeutic dose, of antibody tagged with a radioactive isotope -- currently Iodine-131. The appropriate radiation dosimetry is complex and outside the realm of traditional dosimetric protocols. The dosimetry and radiobiology of this treatment modality require intensive study and constitute a major research program.

As a starting point for the study, we will use the medical internal radiation dose (MIRD) formulation of the Society of Nuclear Medicine as the basis for calculation, with various assumptions. The actual numerical computations are performed using programs obtained from Oak Ridge National Laboratory (MIRDOSE package, revised January 1988 version) and run on IBM-compatible hardware.

ELECTRON-BEAM-ENERGY MONITORING USING A STAIRCASE FILTER

Investigators: P.F. O'Brien, B.A. Gillies and R. McVittie

Quality-assurance measurements for linear accelerators with electron-beam capability must include a check of electron-beam energy. Such a program also would include measurements of beam uniformity and accelerator output or calibration factor. Previously we developed a technique for measuring the effective energy over the entire electron field. When two large transmission chambers were separated by a wedge of polystyrene, changes in energy produced a change in the ratio of ionization chamber readings. One drawback to this procedure is that changes in beam uniformity would also produce a change in the measured ratio and we could not separate these effects.

For a routine procedure, the energy measurement must be rapid and yet must be reproducible; the technique should be sensitive enough to detect a 1% shift in energy -- corresponding to a practical range shift of about 1 mm at 20 MeV. Using the Princess Margaret Hospital/Toronto-Bayview Regional Cancer Centre matrix dosimeter, we have devised a quality-assurance procedure that measures quickly and reliably the output, field uniformity and beam energy. Measurement of relative beam energy, which is independent of field symmetry and flatness, can detect changes in the shape of the depth-dose curve that other techniques may miss. This computer-driven procedure stores results on floppy disks. The technique for energy monitoring is sufficiently sensitive to detect a change in effective energy of 0.1 MeV (1 standard deviation) corresponding to a range shift of less than 1 mm. In linear accelerators at our Centre, energy monitoring showed that generally beam energy does not change more than 0.2 MeV.

This technique will improve our quality-assurance program and will provide information to characterize and optimize beam parameters, critical for accuracy in radiotherapy.

EFFECT OF ELECTRON AFFINITY ON RADIOLYTIC OXYGEN DEPLETION IN SOLUTIONS OF NITROAROMATIC RADIATION SENSITIZERS

Investigator: H.B. Michaels

Studies have continued on mechanisms of action of radiation-sensitizing drugs on hypoxic cells. Under certain conditions, these drugs interfere with the depletion of oxygen by radiation. These effects have been observed in irradiated aqueous solutions and in mammalian cells. Experiments have been extended to nitroimidazole and nitrofuran derivatives of widely varying electron affinity. During irradiation, the oxygen concentration in sealed solutions was monitored continuously with a sensitive oxygen electrode. We observed significant protection of oxygen from radiolytic depletion in concentrated solutions of nifurpipone -- the most electron-affinic drug studied, but found no such effect with metronidazole -- the least electron-affinic compound. The results are consistent with a model we developed earlier to explain the interaction of sensitizer and oxygen depletion on the millisecond time scale.

CLINICAL PHARMACOLOGY

Investigators: I.G. Kerr, P. Bunting, C. DeAngelis, C. Erlichman, R. Feld, M. Moore and J. Thiessen

The Toronto Oncologic Pharmacology Program was developed to carry out clinical pharmacology studies of anticancer drugs, antiemetics, antibiotics and analgesics used by patients with cancer. The aim of the program is to develop a better understanding of drug therapeutics using pharmacologic techniques. Studies involving available and new drugs, e.g. Phase I, are underway.

PIGMENTED SKIN LESIONS AND MALIGNANT MELANOMA

Investigators: N. Iscoe, L. From, M. McKenzie, J. Gruss, J. Phillips and S. Hume

A computer-base registry has been established to monitor the clinical course of all patients with malignant melanoma, and those with dysplastic nevi requiring whole-body photographs registered at the Toronto-Bayview Regional Cancer Centre. To date, we have entered over 1000 patients with melanoma and approximately 200 requiring whole-body photographs for dysplastic nevi. The databank will permit statistical examination of such issues as prognostic factors in melanoma, the impact of excision width on recurrence rates, and the malignant transformation rate of melanoma. A study of VP-16, cis-platinum chemotherapy has been commenced in those patients who have developed metastatic melanoma.

DIGITAL FILM DENSITOMETRY

Investigators: R. Barnett, J. Tobia and V. Velocci

A digital system has been developed to permit the rapid analysis of optical density from radiographic film. This is useful when measuring percentage depth dose and relative isodose profiles for high energy x-ray and electron beams used for radiotherapy.

The system consists of a variable-intensity illuminator, a densitometric vidicon camera with a wide-angle lens, and a digital processing interface "frame grabber" to an IBM personal computer. For analysis we used a Compaq-386 computer with a 20 MHz math coprocessor.

An exposed film is imaged by the vidicon, digitized by the frame grabber, and stored as an array of pixels. Each pixel represents a logarithmically scaled optical transmission. The spatial resolution is a function of the image size but the largest pixel dimension is less than 0.4 mm. Currently, the maximum image diameter is limited to 15 cm.

The system's excellent spatial resolution is particularly useful for small-field applications, such as stereotactic radiosurgery where typically the beam diameter is 1 cm.

The analysis software allows the user to select and store optical density profiles along arbitrary directions. Isodensity levels can be generated and stored on file. One can calibrate the system by exposing films to known absorbed doses and establishing an absorbed dose versus optical-density curve. Then the optical-density information is converted via the calibration curve to absolute dose.

ANTIBODY GUIDED INTRACAVITARY RADIOIMMUNOTHERAPY FOR MALIGNANT EFFUSIONS: THE COLLABORATIVE RESEARCH IN OVARY GROUP

Investigators: R. Buckman, A. Marks, P. Shaw, R. Reed, G. Mills, H. Michaels, I. Kerr, R. Reilly, J. Law and C. DeAngelis

Since 1985 this group has been investigating the use of H_{-I} radiolabelled monoclonal antibodies for intracavitary injection in the treatment and evaluation of malignant effusions.

We screened a panel of 14 antibodies against tumor cells obtained from effusions. From the panel, one antibody (2G3, Cetus Laboratories, California) was selected because of its consistent reactivity with all effusions of breast or ovarian origin, its high density and uniformity of stain, and its relatively low crossreactivity with normal tissues (*Tumour Biol* 1988; **9**: 101). We investigated different protocols of radiolabelling, purified the antibody and did pyrogen-testing of the conjugate. Five patients have received tracer doses (2mCi or less) of radioconjugate instilled through an intraperitoneal catheter. Dosimetry has been done on quantified counts obtained by an external gamma-camera, and counts obtained from ascites, blood and urine. Also, we have obtained autoradiograms, serum and ascitic levels of the 2G3 antigen and human-anti-mouse-antibody levels. The complex dosimetric calculations are still in progress. Four of the five patients, who had a satisfactory distribution of conjugate, received treatment doses (from 7mCi to 25mCi) as part of the group's Phase I study. Systemic and local toxicity has been negligible, but at these low doses no responses have been seen.

The Phase I study continues with I-131 but we are studying methods using yttrium Y-90 in order to reduce radiation hazard to patients and staff.

This work has been supported by a grant from Physicians Services Incorporated.

INTRAPERITONEAL THERAPY

Investigators: I.G. Kerr, R. Buckman, C. DeAngelis, H. Michaels, R. Reed and P. Shaw

Work in progress is investigating the intraperitoneal administration of chemotherapy and monoclonal antibodies tagged with radioisotopes in malignant ascites and ovarian cancer. In addition, the monoclonal antibody technology is being used to type cancer cells in malignant effusions.

OUTPATIENT NARCOTIC INFUSIONS

Investigators: I.G. Kerr, M. Sone, B. Doan, C. Coons, C. DeAngelis, F. Ferris, R. Gray and H. Wodinsky

Although most cancer pain can be managed with oral narcotics, selected patients may need outpatient narcotic infusions. We have developed an outpatient narcotic infusion program, using portable infusion pumps, which incorporate the benefits of continuous drug infusions and patient-controlled analgesia. This program will benefit patients with poorly controlled cancer pain, who cannot tolerate high doses of oral narcotics because of side effects or who, because of dysphagia or bowel obstruction, cannot ingest high doses of narcotics. The pump also allows patients with poorly controlled pain to die at home without lengthy preterminal hospitalization. Work in progress is developing better methods of pain assessment and is examining the pharmacology of morphine and hydromorphone.

Division of Epidemiology and Statistics, Toronto

EPIDEMIOLOGY RESEARCH UNIT[*]

E.A. CLARK[**], E. HOLOWATY[†], N. KREIGER[††] and L.D. MARRETT[‡]
Toronto, Ontario

Since 1978, the Epidemiology Research Unit of the Division of Epidemiology and Statistics has been affiliated with the Department of Preventive Medicine and Biostatistics at the University of Toronto. The Unit was established to conduct analyses using the cancer-data bases of the OCTRF, to assess the quality of these data, to provide cancer research workers with epidemiological and biostatistical assistance, to conduct or support cancer research projects, and to provide information to the general public and the scientific community to increase their understanding of cancer.

Members of the unit, holding academic appointments at the University, are Drs. E.A. Clarke, E. Holowaty, N. Kreiger and L.D. Marrett. Other staff members are G. Cameron, I. Fan, J. Fleury, S. Hilditch, N. Ryan and M. Swift.

The Unit provides the site for many of the externally-funded research projects of the Division of Epidemiology and Statistics. Recently, etiologic case-control studies of breast cancer, malignant melanoma, renal-cell carcinoma, and thyroid cancer were conducted here. Many of these studies used the Ontario Cancer Registry to identify cases and involved collaboration with other investigators and agencies.

Staff of the Unit have participated in many projects based on the Ontario Cancer Registry, such as an analysis of completeness of cancer registration through application of "capture-recapture" techniques; analysis of survival of Hodgkin's disease patients; preparation of a cancer mortality atlas for Ontario; and ascertainment of the cancer experience of a cohort of patients receiving cardiac catheterization.

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[*] Project 381.

[**] Head, Division of Epidemiology and Statistics, Ontario Cancer Treatment and Research Foundation; and Associate Professor in the Department of Preventive Medicine and Biostatistics, University of Toronto.

[†] Head, Cancer Registration Unit, Division of Epidemiology and Statistics, OCTRF; and Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T.

[††] Head, Statistics Section, Division of Epidemiology and Statistics, OCTRF; and Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T.

[‡] Director, OCTRF Epidemiology Research Unit; and Assistant Professor in the Department of Preventive Medicine and Biostatistics, U of T.

Analyses are being carried out using data collected during case-control studies conducted by senior Epidemiology Research Unit staff in past years. These include examination of the association between cigarette smoking and endometrial cancer; the relationship between cervical neoplasia and oral contraceptive use; the interaction between cigarette smoking and herpes virus type II infection in the etiology of cervical cancer.

There has also been extensive development of microcomputer software to display the data being generated by the Ontario Cancer Registry. These include graphs of time trends in the incidence or mortality of various types of cancer; maps of cancer mortality by county; calculation of rates for specified subgroups of patients; etc. These have been useful in investigating the patterns of cancer in Ontario.

Finally, those with academic appointments have been involved in teaching of undergraduate medical students and graduate students (M.Sc. and Ph.D. candidates) in epidemiology.

This project is supported by the OCTRF.

ADDITIONAL INVESTIGATIONS

Dr. E.A. Clarke, Head of the Division of Epidemiology and Statistics, reports on the following studies:

SECOND MALIGNANCIES IN CYTOTOXIC THERAPY

Investigator: E.A. Clarke

This case-control study will examine the relationship between cytotoxic treatment and the risk of developing second primary cancers. It focuses on three cancer sites, namely, Hodgkin's disease, ovarian cancer and testicular cancer, because chemotherapy is used extensively in these tumors and an appreciable fraction of the patients survive long enough to be at risk of a second cancer. This is an international collaborative study.

All patients resident in Ontario and diagnosed with Hodgkin's disease, ovarian cancer or testicular cancer (index cancers) between January 1, 1964 and December 31, 1983, were eligible for inclusion in the Ontario portion of the study, if earlier they had not had another cancer (excluding non-melanotic skin cancer). Eligible subjects were identified from the records of the Ontario Cancer Registry.

We accepted as "cases" those with Hodgkin's disease, who developed leukemia (26) or lung cancer (14); ovarian cancer, who developed leukemia (14) or bladder cancer (0); or testicular cancer, who developed leukemia (2) or bladder cancer (0). From the remaining eligible patients we selected three controls for each case according to the following criteria: (a) the index cancer was the same as that of the case; (b) the sex was the same as that of the case; (c) the age was within three years of that of the case; (d) the date of diagnosis of the first cancer was within five years of that of the case; (e) survival from diagnosis of the index cancer was at least as long as the period between diagnosis of the first and second cancers in the case; and (f) no other second cancer (other than non-melanotic skin cancer) was recorded during the period defined in (e).

Information on chemotherapy and radiation for the 56 cases and 168 controls was abstracted from records of the Ontario Cancer Registry, the OCTRF regional cancer Centres, and the Ontario Cancer Institute incorporating the Princess Margaret Hospital, and hospitals and physicians. All information has been forwarded to the International Agency for Research on Cancer in Lyon, France, where statistical analyses are underway based on data from Ontario and other study centres.

This project is funded by the International Agency for Research on Cancer.

CANCER RISK DURING CARDIAC CATHETERIZATION

Investigators: E.A. Clarke and S. Hilditch

Children with congenital heart disease, who undergo cardiac catheterization, may receive significant radiation exposure from multiple chest fluoroscopies. This study evaluates the risk of cancer in later life among those with childhood exposure to cardiac catheterization compared to the general population.

Patients who were catheterized at the Hospital for Sick Children (HSC) between 1950 and 1965 will be linked manually with the Ontario Cancer Registry incidence file (1964-1985) and with the Ontario death file (1950-1985). Rates of cancer in these patients will be compared with those of the general population. If an excess risk of cancer is identified in the catheterized group, a "nested" case-control study may be conducted to assess in more detail the factors associated with risk.

Study subjects have been identified from computerized data files at HSC. Approximately one-half are females, who were last seen at HSC when under 19 years of age. Since many of these women will have married and changed their surnames since that time, Ontario marriage license files are searched to ascertain married names of those who survived beyond the age of 16 (as determined from HSC records). Linkage with cancer incidence and mortality files can then employ both maiden and married names.

Linkages with cancer files are underway.

This project is funded by the Atomic Energy Control Board.

CHILDHOOD LEUKEMIA AROUND NUCLEAR FACILITIES

Investigators: E.A. Clarke, T.W. Anderson and J.R. McLaughlin

This study will determine whether clusters of childhood leukemia exist in children born to mothers residing in the vicinity of major nuclear facilities in Canada -- the majority of which are in Ontario. It was initiated in response to findings in the U.K. of childhood leukemia clusters near two nuclear-power installations.

All children, aged 0-4 years, who died from or developed leukemia have been identified from both the mortality file (1950-1986) and the incidence file (1964-1985) of the Ontario Cancer Registry. The birth certificates of these children were used to determine the mother's residence at time of the child's birth. The annual number of live births by mothers' residence in the counties of interest are being obtained from Ontario Vital Statistics and we will calculate the rates of leukemia in relation to live births for these counties and compare them with the provincial rate. If this suggests an elevated risk, the study may be extended to include leukemias in children aged 5-14 years or all cancers in children aged 0-4 years.

This project is funded by the Atomic Energy Control Board.

LEUKEMIA AFTER RADIOTHERAPY FOR UTERINE CANCER

Investigators: E.J. Holowaty and P. Toogood

This population-based case-control study has been designed to evaluate the risk of a second cancer -- leukemia (all forms) among women treated with radiotherapy for uterine corpus cancer. This study is being conducted by the Radiation Epidemiology Branch of the National Cancer Institute (NCI) in Bethesda, in collaboration with population-based cancer registries in Ontario, Los Angeles, Iowa, Michigan, Connecticut, Denmark, Finland and Norway.

Women diagnosed with invasive histologically-confirmed cancer of the uterine corpus during 1964 and 1985 inclusive, who survived a minimum of 12 months, are eligible for this study. The uterine corpus cancer must have been their first cancer diagnosed. Except for non-melanoma skin cancer, previous cancers (either in situ or invasive) disqualify women for the study. The women must also have been residents of Ontario at the time of the uterine corpus cancer diagnosis. Cases will be selected from the subjects who have been diagnosed with leukemia (histologically confirmed) 12 months or more after diagnosis of uterine corpus cancer. They must have no other intervening cancer.

Five controls will be matched to each case, based on date of diagnosis of uterine corpus cancer, age, and duration of leukemia-free survival.

From the Ontario Cancer Registry database, it has been determined that 17,000 subjects with uterine corpus cancer are potentially eligible for this study. Of these, it is estimated that approximately 40 subjects with a second leukemia will meet the case-selection criteria.

Relevant study information, including the subject's medical history, uterine corpus cancer diagnosis, uterine corpus cancer treatment, other treatment, other medical procedures, vital status, reproductive history and other cancer diagnoses (including leukemia), will be abstracted from the appropriate hospital and clinic records. Photocopies of radiotherapy records, confirmatory pathology reports, and slides supporting the diagnosis of leukemia, will be forwarded to NCI.

The data collection phase of this study began in January 1988 and will be completed by September 1988.

This project is supported by the National Cancer Institute, Bethesda, Maryland.

RADIATION EXPOSURE AND BONE CANCER

Investigators: N. Kreiger, M. Finkelstein and P. Beck

This population-based case-control study will provide information on the risk of bone cancer associated with radium content in drinking water. It also will address the risks associated with other factors, including prenatal and early childhood exposures. This case-control epidemiologic study has two arms: one will concentrate on investigating the association between bone cancer and radium in drinking water; the other will examine the effects of several other potential risk factors. Cases comprise patients 25 years of age or younger diagnosed with bone cancer in the Province of Ontario. They will be identified through reports submitted to the Ontario Cancer Registry (OCR) between the years 1964 and 1988. There will be two control groups: one identified through OCR records, the other selected through random digit dialing of the telephone. Controls will be the same age and sex as the cases.

Mothers of subjects diagnosed before 1980 will be sent a brief questionnaire concerning their residence history; mothers of subjects diagnosed since 1980 will be sent a more detailed questionnaire regarding the subjects' prenatal and childhood exposures. With the knowledge of the subjects' mothers, water samples will be taken at their previous residences. Statistical analysis will be done to ascertain differences between cases and controls.

Identification of study subjects and design of the mailed questionnaire are underway. A microcomputer data management system is being developed, and preliminary work has begun on procedures for random digit-dialing for control selection.

OCCUPATION/CANCER DATABASE

Investigator: L.D. Marrett

The ultimate goal of this project was to recommend ways in which a useful occupation/cancer database could be established economically in Ontario, using the Ontario Cancer Registry.

Various possibilities became obvious after review of literature, discussions with others who have attempted to set up a population-based occupation/cancer database, and discussions with holders of potentially useful databases. Recommendations have been made to the funding agency and await action.

This project is funded by the Industrial Disease Standards Panel, Ontario Ministry of Labour.

OCCUPATIONAL EXPOSURE IN MALIGNANT MELANOMA

Investigators: S.D. Walter, L.D. Marrett, L. From, C. Hertzman and H.S. Shannon

This study was undertaken in response to the rapidly rising incidence and mortality from malignant melanoma of the skin and to report that occupational exposure to fluorescent light may increase the risk of cutaneous malignant melanoma.

We interviewed in person all those with primary cutaneous malignant melanoma newly diagnosed between October 1, 1984 and September 30, 1986, in a six-county region of southern Ontario. They were asked about their constitutional characteristics -- hair, eye and skin color, number of nevi, skin reaction to sun, residential and occupational histories, use of sunlamps and sunbeds, usual patterns of vacation and leisure activities, and use of selected medications. We gathered the usual demographic variables and also asked about residential and occupational exposure to fluorescent lighting. A population-based sample of controls was likewise interviewed. Also we interviewed patients referred to a pigmented-lesion clinic, who were referred for biopsy before they knew their diagnosis, to permit us to assess the role of recall bias.

Data have been collected on 615 cases and 608 controls and analysis is proceeding. To date, we have found an elevated risk for use of sunlamps and sunbeds; a slightly increased risk associated with domestic and occupational fluorescent light exposure, particularly in men; no association with vacation history or outdoor leisure activity; and the usual associations with large numbers of nevi, fair coloring, and tendency to burn rather than tan.

Funding for this project was obtained from the National Cancer Institute of Canada, and the National Health Research and Development Program of Health and Welfare Canada.

RENAL-CELL CARCINOMA IN ONTARIO

Investigators: L.D. Marrett, N. Kreiger, L. Dodds and S. Hilditch

A case-control study of the etiology of renal-cell carcinoma in Ontario was initiated in 1986. We sent patients with newly diagnosed cancer for the period 1986 and 1987 a brief questionnaire requesting information on smoking, and dietary habits, occupational exposures, use of analgesic and diuretic medications, and basic demographics. A random sample of the population, selected from enumeration records held by the Ontario Ministry of Revenue, were sent the same questionnaire. Nearly 90% of cases and 74% of population controls responded (these represent very high rates of response for this type of survey).

Data collection is completed (517 cases and 1369 controls). Analysis to identify risk factors for this aggressive disease will be undertaken through the end of 1988 and early 1989. It is to be hoped that ultimately risk factor modification will lead to a reduced incidence of renal-cell carcinoma.

This project is funded by the Ontario Ministry of Health.

HUMAN PAPILLOMAVIRUS

Investigators: W.E. Rawls, L.D. Marrett and A. Worth

This study employs the database of the British Columbia Cervical Cytology Registry and a case-control design to determine whether the presence of certain types of human papillomavirus (HPV) will predict progression from cervical intraepithelial neoplasia (CIN) to invasive cervical cancer.

The cases were women who developed invasive cervical cancer more than two years after a diagnosis of CIN -- as recorded in the cytology registry. For each case, two controls were selected; these had a diagnosis of CIN of the same grade in the same year as the case but did not have cervical cancer during the period of follow-up. Presence of HPV types at time of CIN diagnosis was determined from biopsy material of all cases and controls.

Analysis showed no significantly elevated relative risks for progression to cervical cancer in association with any type of HPV, although the data suggested a role for HPV 6/11 and HPV 18. Problems with HPV assay, particularly in "old" tissue, and small sample size make interpretation of results difficult.

University of Toronto

AN IN VIVO AND IN VITRO IMMUNO-ELECTRON MICROSCOPE STUDY OF UROTHELIAL DIFFERENTIATION*

B.K. CHOI **, E.P. DEHARVEN†, W. HANNA†† and J.G. CONNOLLY‡
Toronto, Ontario

The prognosis of low-grade, papillary, transitional-cell carcinoma of the bladder remains difficult to establish. Twenty-five per cent of patients progress to invasive cancer; current methods of identifying this sub-group is unsatisfactory. We have been using new methods of immunoscanning electron microscopy to identify antigens expressed on the cells of the bladder's luminal surface. We seek to obtain new data which will prove to be of prognostic value and will enable us more readily to identify patients at high risk for progression of their disease.

Our aim is to define the phenotype of the superficial cells of the normal and malignant urothelium, using new methods of immunoscanning electron microscopy. The deletion of ABH blood group antigens will be correlated with the appearance of tumor-associated antigens (TAAs) in double-labeling experiments. We will determine whether the cells which lose expression of ABH antigens are those which acquire various TAAs. Our preliminary results, using the LEU-M1 and OM5 mAbs, provide encouraging results in this respect. We have access to a panel of monoclonal antibodies -- some expressed on superficial tumors, others on infiltrating cancers.

In vitro studies will permit us to determine the quantitative value of immunogold labeling. For that purpose, we have chosen the EGF receptor as a model system, for the following reasons 1) the availability of cell lines expressing known and different amounts of EGF, and 2) recent reports on high levels of EGF receptor in invasive bladder tumor.

Retinoids suppress development of the malignant phenotype and hence are used for chemoprophylaxis of patients at high risk of developing bladder cancer. Still, a paradoxical situation exists: retinoids enhance the number of available EGF receptors on the surface of many cultured cells. Therefore, we shall attempt to resolve this paradox, studying the phenotype of cultured bladder cells, grown in presence of all trans-retinoic acid.

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* RA-201.

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FACTORS AFFECTING URINARY MUTAGENIC LEVEL OF WORKERS WITH BLADDER CANCER*

B.C.K. CHOI** and J.G. CONNOLLY†, *Toronto, Ontario*

The purpose of this study is to evaluate the usefulness of urinary mutagenicity screening as a method to identify workers in high-risk industries who may have bladder cancer. We also seek to determine the range of urinary mutagenicity activity and screening levels -- cut-off points for decision making, which maximize the usefulness of the test.

We are investigating 40 bladder-cancer patients and 40 controls from teaching hospitals including the Princess Margaret Hospital in Toronto. An epidemiologic interview with each patient includes an occupational history and some details about possible exposure to industrial chemicals. Two specimens of urine are obtained from each subject, the first taken while the patient is in the work environment, and the second 48 hours out of that environment. The urines are concentrated and urinary mutagens are extracted. To determine the urinary mutagenic levels, we employ the Ames/Salmonella Microsome Plate Assay, using two bacterial strains Ta98 and TA100, with and without S-9 activation.

We will do two main types of data analysis. The first determines the correlation between the degree of potency of the mutagen in the urine and the type of bladder cancer. Secondly, we will determine if there is a dose-response relationship between urine mutagenicity, the degree of invasiveness of the cancer and its biological behaviour while under observation and treatment.

The investigators are endeavoring to establish whether a basis exists for performing urinary mutagenicity testing in workers who may be exposed to mutagenic substances. Also, we wish to determine whether such a testing is useful in the evaluation of individuals who have bladder cancer, and in whom the disease may be due to workplace exposure to mutagens.

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MECHANISM OF CANCER REVEALED BY A RARE TUMOR OF CHILDREN*

B.L. GALLIE**, *Toronto, Ontario*

The study of rare childhood eye cancer -- retinoblastoma -- revealed a fundamental mechanism in the development of malignancy[1]. When a mutation of a specific gene on chromosome 13, RB1, occurs in one allele on one chromosome of germinal cells, the child develops normally, as long as the other chromosome has a normal RB1 allele. In 1983, the Toronto retinoblastoma group, lead by R.A. Phillips and B.L. Gallie, and others[1,2], recognized that tumors develop when the remaining normal allele is also damaged, by loss or another mutation. A child with a germinal RB1 mutation is prone to develop several types of tumors: multiple retinoblastoma tumors usually involve both eyes, and bone and other tumors may develop later in life[3]. Also children with two normal RB1 alleles can develop retinoblastoma but, in those instances, both RB1 alleles become mutated in one retinal cell: the children have only one tumor and are not at increased risk for other cancers. The retinoblastoma studies suggest that cancer forms when both copies of a normal gene are mutated, and frequently this occurs through loss of the normal and duplication of the mutant chromosome[1]. Therefore it can be considered that the RB1 gene normally "prevents" cancer; malignancy develops in the absence of the product of such an "anti-oncogene".

The existence of other anti-oncogenes in different cancers was then anticipated. In various types of cancer, we found different specific chromosomal regions, which in the tumor cells had lost the normal variability of two alleles, each inherited from one parent. Such regions are candidates to contain anti-oncogenes, which normally might prevent malignancy in specific cell types, for example: chromosome 3p for lung and kidney cancer, chromosomes 11 and 13 for breast cancer, and chromosome 13 for bone cancer[3], such as Terry Fox developed.

In 1986, Friend and co-workers[4], cloned the anti-oncogene, RB1, mutations of which lead to retinoblastoma tumors. By standard techniques, the cloned probe revealed that RB1 was abnormal in 20% of retinoblastoma tumors[5]. Dunn et al, of the Toronto Retinoblastoma Group, showed that mutations of RB1 can be identified in more than 50% of retinoblastoma tumors, using a more sensitive technique known to reveal about one-half of small, single-nucleotide mutations[6]. In addition, a mutation was identified in the normal, non-tumor cells of a child with retinoblastoma affecting both eyes. This is the best evidence yet available that the cloned gene is RB1.

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Other workers have found that tumors not suspected to be linked to retinoblastoma, such as breast and lung cancer, also may contain RB1 mutations[7,8]. The more vigorously the cells grow, the more likely they are to have mutations in RB1, suggesting that loss of normal RB1 function may permit more rapid cell division not just in retinoblastoma, but in many types of tumor.

Studies of DNA sequence and the predicted amino-acid sequnce of RB1 revealed no similarities to known proteins. However, a similarity was noticed between the size of the RB1 protein and the presence of a nuclear protein bound by the tumor-inducing product of the DNA viruses -- adenovirus[9], SV40[10], and papillomavirus. Comparisons then showed that these proteins were identical: the DNA tumor viruses appear to induce malignancy in mammalian cells, at least in part, by inactivating the RB1 protein.

The cellular function of the RB1 protein is unknown. We can postulate that RB1 either stimulates production of a protein that allows a cell to respond to growth control signals, or inhibits production of a protein that promotes cell division -- an "oncogene". In either case, absence of the normal RB1 protein contributes to malignancy: in a developing retinal cell, retinoblastoma may be initiated; in tumors initiated by other mechanisms, loss of RB1 may further promote proliferation. The DNA tumor viruses have taken advantage of the key role of RB1 in control of cell proliferation, to promote cell division by interfering with the function of the RB1 protein.

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THE CARCINOGENIC POTENTIAL OF PHOTOSENSITIZERS: RELATIONSHIP OF PHEOMELANIN AND PSORALENS IN SKIN CANCER*

H.F HABERMAN** and I.A. MENON†, *Toronto, Ontario*

We have continued investigations on the etiology of skin cancer, with special emphasis on the role of pheomelanin and photosensitizing drugs, in combination with ultraviolet radiation. Our previous studies have shown that pheomelanin is chemically different from eumelanin, and that UV-visible irradiation of pheomelanin produces superoxide, hydrogen peroxide and enhanced free radical contents. Irradiation of cell suspension in the presence of pheomelanin produced cell lysis.

As an extension of these studies, ultrastructural changes were investigated in the cells before irradiation with pheomelanin. We observed that pheomelanin particles penetrated the cell membrane without apparent structural damage. Irradiation of the cells in the presence of pheomelanin produced extensive ultrastructural changes before complete cell lysis. On the other hand, irradiation of eumelanin or treatment of the cells with pheomelanin produced only minor changes. These studies provide a ready model for demonstrating that one can induce various cellular changes without causing cell death. Therefore it is expected that the photosensitizing effects of pheomelanin in human skin may positively contribute to the UV-induced damage of the skin.

Also we have developed a micro method for determining the type of melanin in the skin samples. Using this technique, the melanins have been characterized in a few preparations of synthetic melanins and in samples from human melanoma.

Also we have studied the phototoxicity of 8-methosypsoralen using an in vitro model consisting of cell suspensions. These studies indicate that psoralen produces photo-induced damage to the cell membrane. We are investigating the contribution of this damage to the carcinogenic effects of psoralens.

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HORMONE RECEPTOR MECHANISMS IN THE DEVELOPMENT AND TREATMENT OF PROSTATIC NEOPLASIA*

G.E. MOBBS**, *Toronto, Ontario*

We have continued to investigate the quantitation, localization, and possible significance of progesterone receptor (PgR) in prostatic tissue. Earlier we reported that the induction of high concentrations of PgR during estrogen treatment of four sublines of the R3327 (Dunning) experimental rat prostatic carcinoma were seen in only the two lines which were well-differentiated and possessed significant amounts of stroma. Now we have been able to show that the well-differentiated, androgen-insensitive HI line progresses during serial passage through castrated rats. In six tumor generations, this tumor increased its growth rate so that the mean time to reach 1.3 cm mean diameter was reduced from 32 to approximately 8 weeks after inoculation. The histopathology changed from well differentiated to poorly differentiated with virtually no stroma, and the cells lost their potential for PgR induction. This model appears to be useful for the study of events which occur during tumor progression. The immunohistochemical localization of PgR using a monoclonal antibody to the receptor indicates that the stroma plays a significant role in determining PgR content. In well-differentiated HI-line tumors treated with diethylstilbestrol, we observed staining for PgR in certain large stromal cells. This was not observed in untreated tumors, or in those in which we used a control antibody for staining.

We have also quantitated PgR in human prostatic tissue biochemically using radioligand assays. In benign tissue obtained at open operation, the mean concentration was 54 ± SD 22 fmoles^{+} per mg cytosol protein (N=18); this was not significantly different from selected tissue from transurethral resections -- 55 ± 32 fmoles per mg protein (N=13). Values in untreated carcinoma were lower [11 ± 11 fmoles per mg protein (N=9)]. However in orchiectomized or estrogen-treated patients, mean values were considerably higher, although variations were large; 57 (range 13-136) fmoles per mg protein, and 105 (range 20-315) fmoles per mg protein respectively for tissue from five orchiectomized and five estrogen-treated patients. This suggests that, as in the Dunning tumors, estrogen treatment is able to induce PgR in some human prostatic carcinomas. The high concentrations of PgR in some of the treated carcinomas, and the Dunning tumor data, support the idea that one might use a cytotoxic progestin as a new type of hormonal therapy targeted at PgR in prostatic carcinomas, which have relapsed after conventional hormonal therapies. We are now investigating this possibility using the Dunning tumor model.

$^{+}$1 fmole = 10^{-15} moles.

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* RA-205-1.

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REGULATION OF EXPRESSION OF EPIDERMAL GROWTH FACTOR RECEPTOR AND ITS LIGAND, TRANSFORMING GROWTH FACTOR-α*

J.E. KUDLOW**, *Toronto, Ontario*

The epidermal growth factor receptor (EGF-R) is a plasma membrane spanning protein, which recognizes either EGF or transforming growth factor-α (TGF-α). The binding of either of these growth factors activates the intracellular portion of the receptor, which is a protein tyrosine kinase. In many human cancers, the simultaneous expression of both EGF-R and TGF-α occurs, thus allowing cells to stimulate their own growth. In a human breast cancer cell line, we have begun examining those factors which regulate the expression of TGF-α and its receptor. We have shown the EGF and tumor-promoting phorbol esters stimulate the synthesis of the receptor and TGF-α by increasing the mRNA for both these proteins. Since TGF-α and EGF have equivalent effects on cells, the ability of EGF to stimulate receptor and growth factor expression implies the existence of a positive feedback system in which growth factor expression drives more growth factor and receptor expression. We have suggested that the effect of EGF on growth factor and receptor expression is mediated by the enzyme -- protein kinase C -- and are testing this notion by transfecting cells with mutant forms of protein kinase C. In addition, we are in the process of cloning TGF-α gene to determine the nature of the regulatory sequences within this gene.

TGF-α expression may also be regulated at the post-translational level because this growth factor is synthesized as a high-molecular-weight precursor which may require extracellular processing. To test this idea, we have transfected cells with the TGF-α cDNA so that the cells synthesize large quantities of the growth factor precursor. We have shown that the conditioned medium of human melanoma cells, when added to the TGF-α transfected cells, causes the rapid release of the growth factor from the cells in association with a loss of the high-molecular-weight precursor on the cells. We are attempting to characterize the TGF-α processing protease secreted by the melanoma cells to better understand the control of its secretion.

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* RS-231.

** OCTRF Research Scholar; and Associate Professor of Clinical Biochemistry and of Medicine, University of Toronto.

Windsor Regional Cancer Centre

CLINICAL INVESTIGATIONS

Dr. G.K. Mok, Director of the Windsor Regional Cancer Centre, reports on the following clinical research investigations:

BREAST CANCER

We continue to enter patients into the OCOG Stage I breast cancer trial and also the NCIC MA-4 trial.

We also participate in the OCOG FEC Stage II breast protocol which has escalating levels of chemotherapy using 5-FU, epirubicin and cyclophosphamide.

We have also received ethics approval of the following protocols for advanced breast cancer:

1. To randomize patients to high-dose epirubicin versus standard-dose epirubicin in patients who have failed CMF treatments.
2. The use of drolixifene for postmenopausal women who are "ER-positive" or "ER-unknown".

CARINOMA OF THE OVARY

We continue to enter patients into the NCIC OV8 advanced Stage III and IV carcinoma of ovary trials, comparing cis-platinum to carboplatin and cyclophosphamide.

ENDOMETRIAL CARCINOMA

This OCOG clinical trial is evaluating medrosyprogesterone and extended-field irradiation in patients with high risk Stage I, II and III carcinoma of endometrium.

HODGKIN'S DISEASE

The Windsor Centre participates in the NCIC HD-4 trial in advanced Hodgkin's disease, randomizing MOPP-ABV hybrid versus MOPP-ABVD. This is for Stage III and IV Hodgkin's disease.

MULTIPLE MYELOMA

This is the ongoing NCIC MY6 clinical trial.

COLORECTAL CARCINOMA

We are participating in the NCIC CO3 protocol using six cycles of 5-FU and high-dose leukovorin versus no treatment.

HAIRY CELL LEUKEMIA

We have ethics approval for the hairy cell leukemia trial randomizing between interferon and pentostatin. However, we have no patients at this point.

LYMPHOMA

We have also received ethics approval for SWOG 8516 trial comparing different regimens -- CHOP versus m-BACOD versus ProMace-CytaBOM versus MACOP-B in advanced, high-grade lymphomas.

EPIDEMIOLOGY AND STATISTICS

DIVISION OF EPIDEMIOLOGY AND STATISTICS

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- K. Rentner, B.Math.
- M. Swift, M.Sc.

Senior Epidemiologist:
- J. McLaughlin, M.Sc.

During 1988, the Division was reorganized in response to the increasingly complex requests for information and other demands placed upon the Ontario Cancer Registry (OCR).

Early in the year, a new Cancer Registration Unit was created, with Dr. E.J. Holowaty at the head. This Unit is responsible for maintenance and development of the OCR. The management responsibility for data coding and entry, manual support of record linkage and many facets of data access falls to Miss D. Dale, the Manager of Operations. Miss A. Chiarelli was hired in September as the new Manager of Development, with the primary responsibility of further enhancing the Case Resolution System, and developing a comprehensive quality control program for the OCR.

A new Provincial Programs Unit has as head, Mrs. M. Nefsky, the former Executive Officer in the Division; she is supported by Mrs. M. Nemes, Manager, Provincial Programs Unit, who continues to interact with the Health Records Departments of the Regional Cancer Centres and the Ontario Cancer Institute/ Princess Margaret Hospital. This Unit has been active in the preparation and revision of a proposal for an organized province-wide integrated program of breast-cancer screening. At the moment, this proposal is under review by the Ministry of Health.

Both the Statistics Section, headed by Dr. N. Kreiger, and the Epidemiology Research Unit, under the direction of Dr. L.D. Marrett, were successful in many grant applications and competitions. It is becoming difficult to locate space for the additional temporary staff working on these studies. The Statistics Section continues to provide information from the OCR to the numerous individuals requesting such. These individuals range from concerned citizens to many different departments associated with government. The Epidemiology Research Unit provides our essential link with the University of Toronto where graphic software is well utilized to visually depict data from the Registry.

In addition, the Division has been strengthened through the appointment of a senior epidemiologist, Mr. J.R. McLaughlin, who shortly will obtain his Ph.D. Mr. McLaughlin's background in survival analysis will be most valuable now that the Ontario Cancer Registry includes all deaths from 1964-1986.

The Division now contains the epidemiology component in the Northeastern Ontario Oncology Program. In addition to her responsibilities for northeastern Ontario, Dr. Van Nguyen, the epidemiologist, is participating in epidemiological studies relating to northwestern Ontario and in studies, using Ontario Cancer Registry data, with other members of the Division of Epidemiology.

In addition to the analyses of cancer incidence and mortality in the Province, the staff of the Division are involved in a number of other projects: Some are collaborative, using Ontario Cancer Registry data, with agencies such as the International Agency for Research on Cancer, others are field studies conducted principally out of the Statistics Section and the Epidemiology Research Unit. All but one of the field studies are supported by peer-reviewed grants.

In 1988, the Division distributed the monograph *Twenty Years of Cancer Incidence in Ontario* to appropriate organizations and institutions within Canada, and to cancer registries in other parts of the world. Many compliments have been received concerning the value and usefulness of this publication.

Following this summary, the most recent data are presented concerning cancer incidence, mortality and treatment in Ontario.

E. Aileen Clarke, M.B., B.S.
Head, Division of Epidemiology and Statistics

CANCER INCIDENCE, MORTALITY AND TREATMENT IN ONTARIO

The Division of Epidemiology and Statistics is responsible for the adequate reporting of cases and the recording and compilation of data: One of the mandates of the Foundation under the Cancer Act. In pursuit of these objectives, the Foundation has maintained and improved a uniform case-recording system which was adopted by the regional cancer centres in 1947 and by the Ontario Cancer Institute incorporating the Princess Margaret Hospital (OCI/PMH) in 1957. The data from the regional cancer centres and the OCI/PMH are in machine-readable form from 1960 onwards. In addition to these records, the Foundation's computerized cancer-data base contains: Individual records on residents of Ontario who died from cancer since 1950; tabulations of deaths by sex, five-year age groups, and type of cancer from 1931 to 1987; individual records of patients diagnosed as having cancer in the Province between 1964 and 1986; individual records of hospital discharges on patients with cancer from 1964 to 1987; and pathology reports on specimens with cancer from 1972 to 1988. The total volume of data base, presently in excess of five million records, provides the Division with a unique opportunity for descriptive cancer epidemiology and allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

CANCER INCIDENCE AND MORTALITY

The Ontario Cancer Registry

The Ontario Cancer Registry now has 23 years of incidence data for the Province and comprises information on more than 600,000 cases of cancer diagnosed in residents of Ontario between 1964 and 1986.

The Ontario Cancer Registry employs a unique system of registration, based on computerized record linkage on cancer cases collected routinely for other purposes and provided to the Foundation. The Registry receives more than 300,000 such records annually. The following province-wide data are routinely forwarded to the Registry:

1. Hospital separations with a mention of cancer collected by the Hospital Medical Records Institute (HMRI) and supplied by the Ontario Ministry of Health; 125,000 computerized records per year.
2. Pathology reports with a mention of cancer submitted voluntarily by hospital pathology laboratories; about 65,000 paper records per year.
3. Reports on patients referred to the regional cancer centres and the OCI/PMH; 20,000 computerized records per year.
4. Deaths from all causes supplied by the Registrar General of Ontario; 65,000 computerized records per year.

Once source files are preprocessed, cancer incidence data are created in two major phases. First, sequential computer linkage of the source files is carried out to bring together all records pertaining to an individual. To connect the large volume of data, the Foundation staff have developed a sophisticated computer record linkage system based on the Generalized Iterative Record Linkage System (GIRLS), designed by Statistics Canada in conjunction with the Epidemiology Unit of the National Cancer Institute of Canada. Then, a set of computerized rules called "case resolution" is applied to the linked records, to determine site of disease, histology, and date and method of diagnosis. Routinely, problems brought to light during either linkage or case resolution are solved by manual resolution.

The generation of cancer incidence data for Ontario is a joint effort of the staffs of the Division of Epidemiology and Statistics and Information Systems who, together, have developed these systems of record linkage and case resolution.

All incidence data presented here are given according to the International Classification of Diseases, Ninth Revision (ICD9). Although between 1964 and 1978, the Registry had coded cancer sites according to the Eighth Revision of the ICD, all records now have been converted to ICD9.

Cancer Incidence and Mortality, 1986

Incidence data are described as "provisional" because they are based only on pathology reports, hospital and deaths records. In 1989, these data will be linked with data from the regional cancer centres. As a result, frequencies and rates here may vary from final statistics on cancer occurrence in Ontario by a few percentage points.

Currently the time lag between cancer diagnosis and publication of incidence data by the Ontario Cancer Registry is about two years. Reporting is delayed until the sources provide essential data, then the Registry must code pathology report, edit and process the files as described. Thus, the most current cancer incidence data, for 1986, are presented in Tables I through IV and Fig. 1. Although *Cancer in Ontario* 1987 gave cancer mortality data for 1986 in Tables V and VI, we show them again in Tables III and IV, and Fig. 1 in this issue, to facilitate comparisons between incidence and mortality for the same year.

Tables I and II give the frequencies by 5-year age group for each cancer site or group of sites, for males and females respectively, for 1986. The far right-hand column gives rank order to identify sites of most frequent occurrence. Fig 1 indicates the frequencies of cancer for selected sites and causes of death for both sexes in 1986. The 10 most common sites, in terms of their sex-specific incidence frequencies, are shown according to their sex-specific incidence frequencies.

Tables III and IV present incidence and mortality rates by age group and site, for males and females respectively, for 1986. In these two tables, the rates for 15-year age groups and for all ages are age-adjusted, using the world standard popula-

TABLE I

Annual Number of New Cases of Malignant Neoplasms in Males by Site of Disease and Age at Diagnosis, Ontario 1986

(Provisional Data*)

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	2	0	0	1	2	8	7	12	18	18	43	66	94	68	58	107	8	512	8
Pharynx	146-148	1	1	0	0	0	1	5	3	2	3	16	33	27	18	19	12	2	143	
Esophagus	150	0	0	1	0	0	0	0	2	4	10	24	37	42	31	25	57	2	235	
Stomach	151	0	0	0	0	0	0	2	7	15	17	34	65	73	95	95	186	1	590	7
Intestine, except rectum	152, 153	0	0	0	0	2	7	14	21	38	59	129	202	262	296	302	484	3	1,819	3
Rectum and anus	154	0	0	0	0	0	3	4	9	6	25	44	83	125	142	135	166	8	750	5
Pancreas	157	1	0	0	1	0	0	2	4	7	17	27	48	71	73	73	122	0	446	
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	1	3	1	1	3	2	10	2	14	0	37	
Larynx	161	0	0	0	0	0	1	0	5	6	13	28	52	72	52	49	55	2	335	
Trachea, bronchus and lung	162	1	0	0	0	2	3	5	19	61	95	213	461	592	638	623	786	2	3,501	1
Bone	170	3	6	7	5	6	5	7	2	2	1	2	5	8	5	9	6	0	79	
Connective tissue	171	4	3	2	5	10	4	5	4	13	9	6	9	12	7	17	19	1	130	
Malignant melanoma of skin	172	0	0	1	6	10	22	26	41	46	29	42	59	61	43	42	68	9	505	9
Prostate	185	0	0	1	0	0	0	2	0	2	10	40	150	316	480	638	1,349	7	2,995	2
Testis	186	6	0	0	10	25	51	47	33	12	11	9	5	7	2	0	3	1	222	
Bladder	188	0	0	0	0	1	2	10	17	31	29	64	124	180	196	213	395	2	1,264	4
Kidney and other urinary	189	7	1	0	0	1	2	4	14	23	17	34	61	68	67	66	88	0	453	10
Brain and other nervous system	191, 192	14	13	8	11	9	13	17	14	29	30	30	35	34	47	28	36	0	368	
Thyroid gland	193	0	0	1	1	4	9	5	11	3	13	7	10	6	6	6	7	0	89	
Lymphosarcoma and reticulosarcoma	200	2	4	5	9	6	8	7	10	17	18	24	25	54	36	41	58	4	328	
Hodgkin's disease	201	0	1	5	11	25	16	13	13	10	9	10	7	8	5	11	10	0	154	
Other lymphomas	202	2	1	3	1	6	6	9	15	14	27	25	39	43	47	34	61	2	335	
Multiple myeloma	203	0	1	0	0	0	0	1	1	3	7	12	19	26	42	39	67	0	218	
Leukemia	204-208	36	11	13	16	9	4	13	14	12	24	38	29	72	68	79	184	3	625	6
Other and non-specific	Residual	25	5	5	2	15	13	10	28	33	57	95	171	216	206	228	406	14	1,529	
TOTAL	140-208[3]	104	47	52	79	133	178	215	300	410	549	997	1,798	2,471	2,680	2,832	4,746	71	17,662	

* See Text.

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977

[2] Rank order for 10 most common sites (or site groups).

[3] Excluding non-melanotic skin cancers (ICD9 number 173)

TABLE II

Annual Number of New Cases of Malignant Neoplasms in Females by Site of Disease and Age at Diagnosis, Ontario 1986 (Provisional Data*)

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DIAGNOSIS (YEARS)																		RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	Age Unknown	All Ages	
Lip and oral cavity	140-145	3	0	2	0	2	5	5	4	4	7	9	33	23	41	25	52	3	218	
Pharynx	146-148	0	0	0	0	0	0	1	4	1	4	4	5	10	9	8	11	0	57	
Esophagus	150	0	0	0	0	0	0	1	1	1	2	2	13	9	12	17	43	0	101	
Stomach	151	0	0	0	0	1	0	2	6	10	12	23	21	34	42	69	165	0	385	
Intestine, except rectum	152, 153	1	0	2	2	3	1	5	20	31	64	86	148	218	274	285	743	5	1,888	2
Rectum and anus	154	0	0	0	0	1	1	4	8	14	25	27	46	57	77	94	227	2	583	6
Pancreas	157	0	0	0	0	1	0	0	4	9	10	16	24	37	57	76	186	0	420	10
Nasal cavities, middle ear and accessory sinuses	160	1	0	0	0	0	0	0	0	0	3	2	2	1	1	5	10	0	25	
Larynx	161	0	0	0	0	1	0	0	2	3	5	7	13	7	12	10	9	2	71	
Trachea, bronchus and lung	162	1	0	0	1	3	3	6	15	36	86	124	195	271	242	231	328	4	1,546	3
Bone	170	0	4	10	4	5	2	2	2	2	1	3	3	2	3	2	6	1	52	
Connective tissue	171	2	1	2	2	3	5	7	2	4	10	6	9	10	5	10	22	0	100	
Malignant melanoma of skin	172	1	0	1	4	24	37	40	46	45	48	40	33	49	27	39	67	5	506	8
Breast	174	1	0	0	0	9	24	100	194	350	367	436	489	542	527	488	839	11	4,377	1
Cervix uteri	180	0	0	0	0	15	46	59	72	44	54	40	45	36	39	31	47	3	531[4]	7
Body of uterus	182	0	0	0	0	1	1	8	8	26	54	86	131	173	189	136	151	0	964	4
Other and unspecified uterus	179, 181	1	0	0	0	2	3	1	5	4	5	5	6	7	7	5	11	0	62	
Ovary and fallopian tube	183	0	0	2	3	5	10	28	23	29	43	62	81	79	70	101	125	0	661	5
Bladder	188	0	0	0	0	1	0	2	5	8	5	21	39	61	55	59	156	0	412	
Kidney and other urinary	189	6	3	1	1	1	3	6	8	15	23	23	38	34	30	50	93	0	335	
Brain and other nervous system	191, 192	12	12	5	11	11	9	16	19	14	14	25	22	35	30	36	52	0	323	
Thyroid gland	193	0	1	1	5	20	27	31	22	27	29	14	19	22	17	20	19	0	274	
Lymphosarcoma and reticulosarcoma	200	0	0	3	4	1	6	5	9	13	9	15	25	43	34	41	81	1	290	
Hodgkin's disease	201	0	1	5	20	20	14	14	8	8	2	3	7	5	7	4	4	0	122	
Other lymphomas	202	1	0	1	1	5	1	10	9	17	21	21	28	26	32	33	62	2	270	
Multiple myeloma	203	0	0	0	0	0	0	2	5	3	4	15	18	26	36	46	70	2	227	
Leukemia	204-208	26	12	12	6	5	10	11	12	9	15	26	27	30	43	47	171	5	467	9
Other and non-specific	Residual	19	3	2	5	8	9	15	39	27	58	65	112	156	163	198	539	6	1,424	
TOTAL	140-208[3]	75	37	49	69	148	217	381	552	754	980	1,206	1,632	2,003	2,081	2,166	4,289	52	16,691	

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* See Text.

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2] Rank order for 10 most common sites (or site groups).

[3] Excluding non-melanotic skin cancers (ICD9 number 173).

[4] Approximately 10% non-invasive cancer of the cervix.

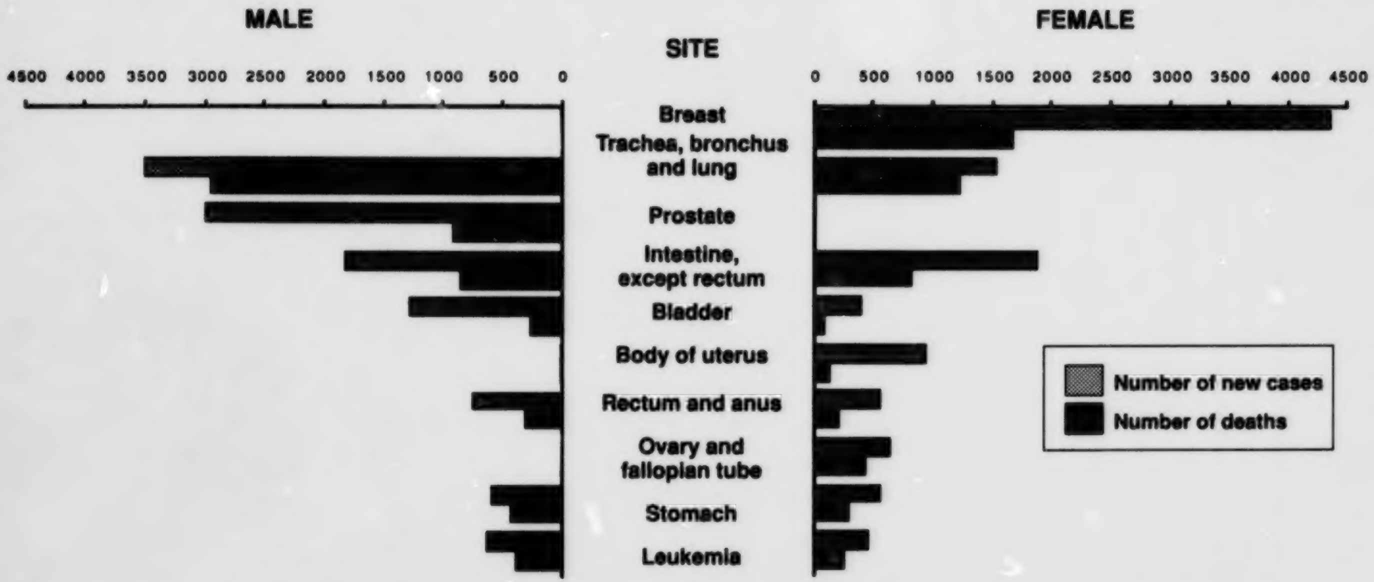

Fig. 1 New cases of, and deaths due to, malignant neoplasms, by sex and site of disease, for common cancers, Ontario 1986.

TABLE III

Age-adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Males, by Site and Age, Ontario 1986

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.2	0.9	3.8	16.9	46.5	76.8	9.2	1.05
		M	0.0	0.0	0.4	4.1	13.8	20.9	2.4	0.28
Pharynx	146-148	I	0.2	0.1	1.0	6.7	13.5	8.0	2.6	0.34
		M	0.1	0.0	0.8	3.6	9.0	6.4	1.7	0.20
Esophagus	150	I	0.1	0.0	0.6	9.5	20.8	40.6	4.2	0.48
		M	0.0	0.0	0.2	9.6	25.6	38.6	4.5	0.53
Stomach	151	I	0.0	0.0	2.5	15.4	54.8	131.3	10.3	1.18
		M	0.0	0.0	1.5	10.8	38.7	104.7	7.5	0.82
Intestine, except rectum	152, 153	I	0.0	0.7	7.5	52.1	179.5	345.1	32.4	3.80
		M	0.0	0.2	3.2	16.1	78.7	222.0	14.6	1.59
Rectum and anus	154	I	0.0	0.2	1.9	20.2	84.1	118.3	13.4	1.70
		M	0.0	0.1	0.7	6.9	28.1	77.1	5.3	0.59
Pancreas	157	I	0.1	0.1	1.4	12.3	45.4	85.7	8.0	0.94
		M	0.1	0.1	1.0	11.7	49.0	101.9	8.5	1.00
Larynx	161	I	0.0	0.1	1.1	12.3	36.5	38.6	6.1	0.77
		M	0.0	0.0	0.1	3.8	12.7	25.9	2.3	0.27
Trachea, bronchus and lung	162	I	0.1	0.4	9.2	100.6	387.6	560.5	63.0	7.70
		M	0.0	0.0	5.4	75.9	327.1	553.1	52.9	6.32
Bone	170	I	1.6	1.4	1.0	1.0	4.6	4.2	1.7	0.15
		M	0.3	1.0	0.3	0.1	2.5	2.3	0.7	0.07
Malignant melanoma of skin	172	I	0.1	3.1	11.4	17.8	30.8	49.3	9.3	1.00
		M	0.0	0.5	2.4	3.8	7.2	12.8	2.0	0.22
Prostate	185	I	0.1	0.0	0.4	25.1	295.0	992.7	50.0	5.36
		M	0.0	0.0	0.0	5.2	69.2	401.4	15.0	1.32
Testis	186	I	0.7	7.0	8.6	3.7	2.0	2.0	4.3	0.32
		M	0.0	0.2	0.5	0.5	0.2	0.0	0.2	0.02
Bladder	188	I	0.0	0.2	6.0	28.6	122.7	282.8	22.1	2.53
		M	0.0	0.0	0.2	2.5	24.3	95.1	4.5	0.45
Kidney and other urinary	189	I	0.9	0.2	4.3	14.9	42.1	61.2	8.4	0.99
		M	0.0	0.0	1.0	7.1	22.8	38.4	4.1	0.48
Brain and other nervous system	191, 192	I	3.7	2.9	6.1	13.4	23.1	24.0	7.5	0.75
		M	0.9	1.1	3.5	10.6	18.3	17.3	4.7	0.51
Thyroid gland	193	I	0.1	1.1	1.8	4.3	3.8	4.8	1.7	0.17
		M	0.0	0.0	0.0	0.7	1.3	1.3	0.2	0.03
Lymphosarcoma and reticulosarcoma	200	I	1.1	2.0	3.5	9.4	27.5	39.2	6.1	0.67
		M	0.0	0.4	0.8	1.7	6.1	15.7	1.3	0.14
Hodgkin's disease	201	I	0.6	4.3	3.5	3.7	4.9	7.3	3.0	0.27
		M	0.0	0.4	1.5	1.0	2.9	2.8	0.8	0.09
Other lymphomas	202	I	0.6	1.0	3.8	12.6	26.2	44.1	6.3	0.68
		M	0.0	0.2	1.6	6.5	22.5	49.0	4.3	0.50
Multiple myeloma	203	I	0.1	0.0	0.5	5.1	22.3	47.6	3.9	0.46
		M	0.0	0.0	0.4	3.4	15.6	39.1	2.8	0.32
Leukemia	204-208	I	6.6	2.7	3.8	12.8	45.6	132.8	12.1	1.12
		M	2.2	2.0	2.4	7.8	27.7	84.4	6.9	0.67
TOTAL	140-208[4]	I	22.0	32.5	93.6	445.5	1665.1	3422.7	316.9	30.50
		M	4.2	7.0	31.1	217.8	902.2	2173.3	166.0	17.06

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.

[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research on Cancer (IARC) Scientific Publication No. 15. pp. 443-52, 1976).

[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

TABLE IV

Age-Adjusted Rates[1] and Cumulative Risks (age 0-74)[2] Incidence (I) and Mortality (M) from Malignant Neoplasms in Females, by Site and Age, Ontario 1986

SITE OF DISEASE	ICD9[3] NUMBER	INCIDENCE/ MORTALITY	AGE AT DIAGNOSIS/DEATH (YEARS)							
			0-14	15-29	30-44	45-59	60-74	75+	All Ages	0-74
Lip and oral cavity	140-145	I	0.6	0.5	1.2	6.3	15.7	21.1	3.3	0.39
		M	0.0	0.0	0.2	1.5	4.3	8.6	0.8	0.09
Pharynx	146-148	I	0.0	0.0	0.6	1.8	4.8	4.5	0.9	0.11
		M	0.0	0.0	0.0	0.5	0.8	1.9	0.2	0.02
Esophagus	150	I	0.0	0.0	0.3	2.1	6.5	16.5	1.3	0.15
		M	0.0	0.0	0.0	2.1	7.6	20.2	1.4	0.15
Stomach	151	I	0.0	0.1	1.9	7.7	24.5	65.4	5.0	0.57
		M	0.0	0.1	1.0	7.0	19.7	48.0	4.0	0.46
Intestine, except rectum	152, 153	I	0.3	0.5	5.8	40.1	134.7	295.7	25.3	2.87
		M	0.0	0.1	2.0	15.3	55.1	150.7	10.7	1.16
Rectum and anus	154	I	0.0	0.2	2.7	13.4	39.1	90.8	7.9	0.90
		M	0.0	0.0	0.3	3.7	15.9	37.6	2.8	0.33
Pancreas	157	I	0.0	0.1	1.4	6.7	28.9	74.1	5.4	0.62
		M	0.0	0.0	0.8	7.4	25.4	85.3	5.2	0.56
Larynx	161	I	0.0	0.1	0.5	3.3	5.0	3.8	1.1	0.14
		M	0.0	0.0	0.1	0.6	2.2	3.0	0.4	0.04
Trachea, bronchus and lung	162	I	0.1	0.6	6.0	54.7	131.2	134.4	24.0	2.95
		M	0.0	0.1	4.0	38.8	109.0	123.5	18.8	2.37
Bone	170	I	1.4	1.0	0.6	1.0	1.2	2.5	1.1	0.08
		M	0.1	0.3	0.0	0.0	0.9	1.2	0.2	0.02
Malignant melanoma of skin	172	I	0.2	5.2	12.7	17.5	20.3	27.1	8.6	0.84
		M	0.0	0.1	1.4	3.0	5.0	4.2	1.3	0.15
Breast	174	I	0.1	2.6	65.9	180.1	274.2	336.3	71.0	7.73
		M	0.0	0.5	16.1	62.1	106.3	187.9	25.7	2.81
Cervix uteri	180	I	0.0	4.7	16.6	19.9	18.7	19.4	9.2	0.90
		M	0.0	0.4	2.2	6.1	10.4	13.5	2.6	0.29
Other uterus	179, 181, 182	I	0.1	0.6	5.4	38.8	91.8	66.5	16.6	2.09
		M	0.0	0.1	0.2	2.0	15.9	27.9	2.3	0.28
Ovary and other uterine adnexa	183	I	0.2	1.5	7.8	25.4	43.1	50.0	10.5	1.23
		M	0.0	0.3	2.1	13.5	37.1	49.8	6.8	0.83
Bladder	188	I	0.0	0.1	1.5	8.4	30.7	61.9	5.6	0.64
		M	0.0	0.0	0.2	0.9	5.7	27.3	1.2	0.12
Kidney and other urinary	189	I	1.2	0.4	2.9	11.5	19.5	36.1	5.2	0.57
		M	0.0	0.0	0.4	2.6	9.7	22.4	1.8	0.20
Brain and other nervous system	191, 192	I	3.3	2.7	4.7	8.5	17.6	21.5	5.8	0.57
		M	0.9	0.7	1.8	6.5	16.3	16.3	3.6	0.42
Thyroid gland	193	I	0.2	4.2	7.7	9.0	10.4	7.5	4.9	0.47
		M	0.0	0.0	0.1	0.3	1.8	4.1	0.3	0.04
Lymphosarcoma and reticulosarcoma	200	I	0.3	1.0	2.7	6.6	20.7	32.9	4.3	0.49
		M	0.1	0.1	0.3	2.0	5.1	7.8	1.0	0.12
Hodgkin's disease	201	I	0.6	4.8	2.8	1.6	2.9	1.6	2.4	0.19
		M	0.0	0.3	0.5	0.9	1.1	3.1	0.5	0.04
Other lymphomas	202	I	0.2	0.6	3.6	9.7	15.8	25.3	4.3	0.47
		M	0.1	0.3	0.8	4.7	12.7	26.7	2.6	0.30
Multiple myeloma	203	I	0.0	0.0	1.0	4.9	18.5	28.2	3.1	0.40
		M	0.0	0.0	0.1	3.1	12.8	23.6	2.1	0.26
Leukemia	204-208	I	5.7	1.8	3.1	9.4	20.7	67.0	7.4	0.64
		M	1.4	1.2	1.6	5.0	13.8	40.0	3.8	0.36
ALL SITES	140-208[4]	I	18.1	35.8	168.3	524.8	1091.2	1716.4	256.1	25.03
		M	3.4	5.3	39.1	205.6	553.2	1111.0	112.2	12.04

[1] Age-adjusted by the direct method to the World Standard Population (See Table VII), expressed per 100,000 persons.

[2] Cumulative risk approximate to the percent probability of a cancer diagnosis/death occurring by age 74 (Reference: Day NE. International Agency for Research of Cancer (IARC) Scientific Publication No. 15. pp. 443-52, 1976).

[3] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[4] Excluding non-melanotic skin cancers (ICD9 number 173). Note that any individual sites not specifically included in the table are included in "ALL SITES".

tion shown in Table VII. The method of direct age-adjustment used here is described by Waterhouse et al in *Cancer Incidence in Five Continents*, vol. 4. Rates in the table have been "age-adjusted" to assist comparisons between the different areas in the world. Age adjustment allows us to account for differences caused solely by differences in age distribution in these areas. The rates in Tables III and IV can be compared with any other rates covering the same age span and using the same standard population for adjustment.

The "cumulative risk" (0-74), shown in the final column of Tables III and IV, is described in detail in *Cancer Incidence in Five Continents*. Expressed per 100, it is a reasonable approximation to the risk (to age 74) of being diagnosed with or dying of the given cancer. Thus, if the current age-specific rates for female lung cancer were to remain unchanged throughout her life, a girl born in 1986 would have about a 3% chance of receiving the diagnosis of lung cancer by age 74. Of course, if age-specific rates continue to rise, the cumulative risk will increase also.

Cancer Mortality, 1987

The most nearly current cancer mortality data are for 1987; these were provided by the Office of the Registrar General of Ontario. Figs. 2 and 3 show the frequencies of death due to malignant neoplasms of all types, relative to other major groups of causes of death among males and females. Tables V and VI give the numbers of cancer deaths by age group at death and site; the same format and groupings are used in Tables I and II for cancer incidence.

Populations

Table VII shows sex- and age-specific population data for Ontario for the years 1986 and 1987, and for the "world standard". These tables provide the 1986 Ontario population (censal) and the 1987 Ontario population (post-censal estimate) for those who wish to calculate age-specific cancer incidence and mortality rates from data given in the previous sections. The world population is an artificial standard, frequently used in the calculation of age-adjusted rates. The Ontario population data are provided by Statistics Canada, and the world population is taken from Cancer Incidence in Five Continents.

CANCER TREATMENT

Hospital Caseload

During the Ontario Ministry of Health's fiscal year 1986-87, active and rehabilitation hospitals in Ontario reported 73,165 separations (discharges and deaths), in

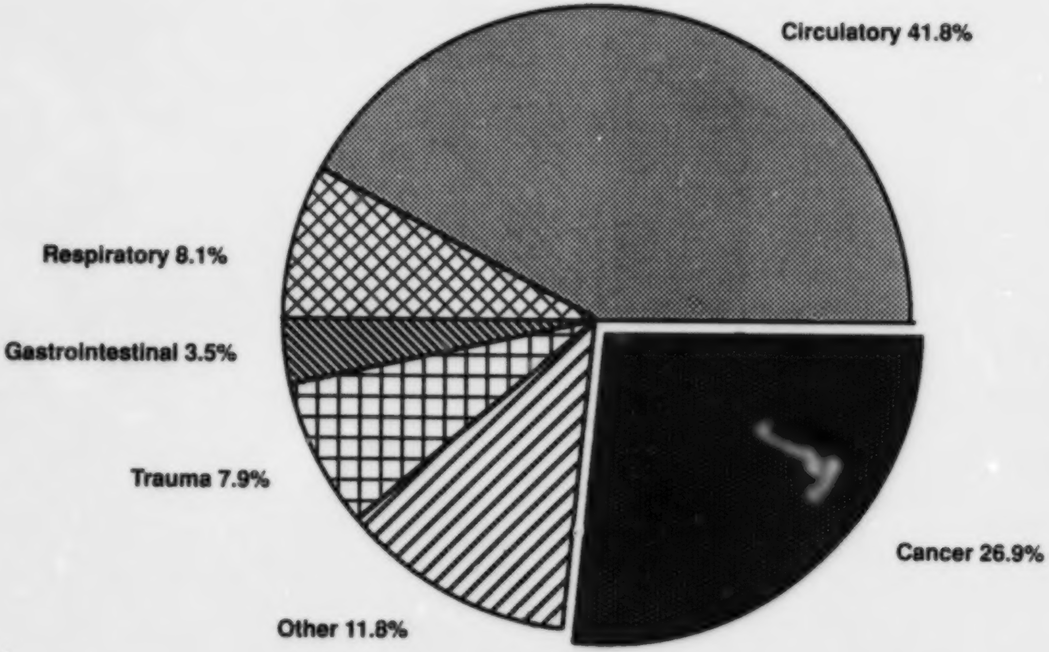

Fig. 2 Percentage distribution of major causes of death in males, Ontario 1987

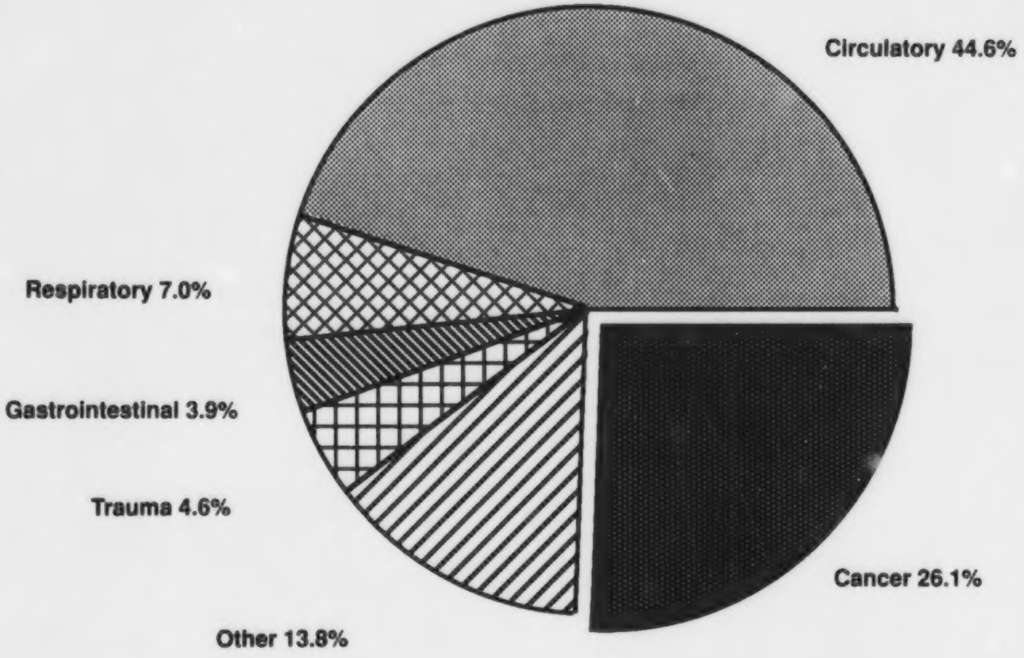

Fig. 3 Percentage distribution of major causes of death in females, Ontario 1987

TABLE V

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario 1987

SITE OF DISEASE	ICD9[1]	AGE AT DIAGNOSIS (YEARS)																RANK[2]
	NUMBER	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral Cavity	140-145	0	0	0	0	0	0	2	3	3	3	11	14	20	23	15	41	135	14
Pharynx	146-148	0	0	0	0	0	0	1	0	1	5	9	19	14	10	10	15	84	
Esophagus	150	0	0	0	0	0	1	2	1	2	11	22	33	46	38	47	75	278	9
Stomach	151	0	0	0	0	0	1	2	1	9	9	22	34	46	79	82	159	444	5
Intestine, except rectum	152, 153	0	0	0	0	1	1	2	6	7	22	35	77	97	162	135	290	835	3
Rectum and anus	154	0	0	0	0	1	1	1	0	3	12	17	27	41	35	43	100	281	8
Pancreas	157	0	0	0	0	0	0	0	5	5	18	28	41	66	54	101	156	474	4
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	2	0	0	1	2	3	3	5	4	20	
Larynx	161	0	0	0	0	0	0	0	1	1	6	6	22	19	20	17	40	132	15
Trachea, bronchus and lung	162	0	0	0	0	0	2	1	11	43	73	183	329	481	572	536	835	3066	1
Bone	170	0	0	3	3	0	1	3	2	1	2	0	2	0	0	1	3	21	
Connective tissue	171	1	1	1	3	0	0	1	1	3	0	3	3	3	4	4	5	33	
Malignant melanoma of skin	172	0	0	0	1	2	2	5	7	8	7	9	13	14	8	9	16	101	16
Breast	175	0	0	0	0	0	0	0	0	1	1	0	2	1	2	1	4	12	
Prostate	185	0	0	0	0	0	0	0	0	0	3	9	26	80	118	216	598	1050	2
Testis	186	0	0	0	0	4	5	3	5	1	1	1	1	0	0	2	2	25	
Bladder	188	0	0	0	0	0	0	0	0	2	2	4	13	27	31	61	167	307	7
Kidney and other urinary	189	0	1	0	0	2	0	2	2	10	9	12	22	30	35	28	59	212	12
Brain and other nervous system	191, 192	5	7	6	2	2	4	8	10	20	14	21	31	36	38	34	23	261	10
Thyroid gland	193	0	0	0	0	0	0	0	1	2	0	1	2	0	2	6	4	18	
Lymphosarcoma and reticulosarcoma	200	0	0	0	2	2	1	0	1	2	3	3	6	8	10	6	17	61	
Hodgkin's disease	201	0	0	0	0	3	1	8	2	0	5	1	4	3	0	6	4	37	
Other lymphomas	202	0	0	1	2	1	3	1	6	3	12	13	14	27	30	52	60	225	11
Multiple myeloma	203	0	0	0	0	0	0	0	2	2	5	9	13	16	27	31	67	172	13
Leukemia	204-208	4	4	7	6	7	5	6	11	7	9	10	27	33	42	58	144	380	6
Other and non-specific	Residual	4	4	1	2	7	11	9	9	17	24	48	94	139	145	187	336	1,037	
TOTAL	140-208[3]	14	17	19	21	32	39	57	89	153	256	478 ,	871	1,250	1,488	1,693	3,224	9,701	

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[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977

[2] Rank order for sites with more than 100 deaths.

[3] Omitted are 38 deaths due to non-melanotic cancers of the skin (ICD9 number 173)

TABLE VI

Number of Deaths due to of Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario 1987

SITE OF DISEASE	ICD9[1]	AGE AT DIAGNOSIS (YEARS)																	RANK[2]
	NUMBER	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	0	1	0	0	0	1	1	1	2	1	2	5	5	8	9	37	73	
Pharynx	146-148	0	0	0	0	0	0	1	1	0	0	2	4	6	3	5	13	35	
Esophagus	150	0	0	0	0	0	0	0	0	2	2	6	5	14	17	18	37	101	16
Stomach	151	0	0	0	1	0	0	2	5	2	7	8	27	24	40	35	121	272	7
Intestine, except rectum	152, 153	0	0	0	0	0	1	3	6	14	25	36	56	75	111	114	419	860	3
Rectum and anus	154	0	0	0	0	0	0	0	2	4	2	7	11	15	27	33	108	209	9
Pancreas	157	0	0	0	0	0	0	0	5	6	13	20	21	46	53	73	191	428	5
Nasal cavities, middle ear and accessory sinuses	160	0	0	0	0	0	0	0	2	0	1	1	2	1	1	3	3	14	
Larynx	161	0	0	0	0	0	0	0	0	0	0	2	4	4	8	5	9	32	
Trachea, bronchus and lung	162	0	0	0	0	0	2	3	13	32	65	99	159	222	213	209	333	1,350	2
Bone	170	0	0	1	2	1	1	1	1	1	0	1	0	0	1	2	2	14	
Connective tissue	171	0	0	0	0	2	0	1	0	1	1	1	2	4	4	5	12	33	
Malignant melanoma of skin	172	0	0	0	0	4	2	2	4	4	3	10	8	9	3	13	20	82	
Breast	174	0	0	0	0	0	4	9	43	103	96	134	184	233	211	212	479	1,708	1
Cervix uteri	180	0	0	0	0	0	3	7	9	12	18	18	9	21	20	17	41	175	12
Other uterus	179, 181, 182	0	0	0	1	0	0	1	2	4	5	10	11	20	39	41	70	204	11
Ovary and fallopian tube	183	0	0	0	2	0	0	3	5	5	27	25	51	66	52	79	138	453	4
Bladder	188	0	0	0	0	0	0	0	0	0	0	2	4	9	8	17	76	116	15
Kidney and other urinary	189	0	1	0	0	0	2	0	2	5	8	6	14	16	19	19	51	143	13
Brain and other nervous system	191, 192	5	5	1	3	2	3	7	9	5	11	15	16	39	19	32	37	209	9
Thyroid gland	193	0	0	0	0	0	0	0	0	0	0	2	0	2	3	3	15	25	
Lymphosarcoma and reticulosarcoma	200	0	0	1	0	0	1	1	0	0	2	3	3	6	5	9	22	53	
Hodgkin's disease	201	0	0	0	1	1	2	0	3	1	1	0	1	5	3	2	4	24	
Other lymphomas	202	0	0	2	0	1	2	1	1	9	5	8	14	25	36	23	107	234	8
Multiple myeloma	203	0	0	0	0	0	0	0	0	1	0	5	7	18	14	23	70	138	14
Leukemia	204-208	8	2	5	2	3	3	3	3	6	7	8	19	21	28	42	139	299	6
Other and non-specific	Residual	1	2	2	2	1	2	5	7	20	21	45	72	100	119	140	480	1,019	
TOTAL	140-208[3]	14	11	12	14	15	29	51	124	239	321	476	709	1,006	1,065	1,183	3,034	8,303	

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977

[2] Rank order for sites with more than 100 deaths.

[3] Omitted are 20 deaths due to non-melanotic cancers of the skin (ICD9 number 173)

TABLE VII

World Standard Population and Estimated Population 1986 and 1987, of Ontario (In Thousands)

AGE GROUP	WORLD STANDARD[1]	ONTARIO, 1986[2]		ONTARIO, 1987[2]	
	MALE OR FEMALE	MALE	FEMALE	MALE	FEMALE
0-4	12.0	323.3	308.1	332.4	316.0
5-9	10.0	311.4	296.8	315.8	301.4
10-14	9.0	323.5	306.3	321.9	305.8
15-19	9.0	352.7	336.4	353.6	335.3
20-24	8.0	408.6	406.0	403.1	397.0
25-29	8.0	406.5	414.6	419.3	425.3
30-34	6.0	372.3	389.6	387.2	402.7
35-39	6.0	362.1	370.2	362.0	371.8
40-44	6.0	292.4	292.3	316.0	316.8
45-49	6.0	244.6	244.1	252.5	252.2
50-54	5.0	231.3	230.1	231.2	230.6
55-59	4.0	226.1	229.7	227.8	230.5
60-64	4.0	202.0	227.9	204.5	228.0
65-69	3.0	151.8	181.9	160.5	192.1
70-74	2.0	118.1	150.8	119.4	153.5
75-79	1.0	75.3	111.7	78.7	115.6
80-84	0.5	41.3	74.4	42.4	77.4
85+	0.5	24.3	63.0	25.4	65.1
TOTAL	100.0	4,467.6	4,633.9	4,553.7	4,717.1

[1] Waterhouse, John et al (eds). Cancer Incidence in Five Continents, Vol IV. World Health Organization, Geneva, 1982, p. 673.

[2] Source: Statistics Canada

which the primary diagnosis was cancer. These accounted for 5.6% of all hospital separations and 1,095,892 days of hospital care. The average length of stay for cancer patients declined from 16.9 days in 1972 to 15.0 days in 1986-87*.

New Cancer Registrations

In the last decade, the number of new cases registered at the regional cancer centres and the OCI/PMH has increased by 43.8% from 16,149 cases to 23,223 (Table VIII). In assessing the significance of these changes over time, one must take into account the introduction in 1979 of the *International Classification of Diseases, Ninth Revision,* which separated the categories -- in situ carcinoma and neoplasms of uncertain behavior -- from malignant neoplasms. In addition, in 1981, the Foundation returned to the international practice of counting patients with skin cancer as having only two lesions --basal-cell or squamous-cell cancer -- and not as having multiple cancers of the same histology in different body sites. The distribution by cancer centre of the numbers of in situ lesions, neoplasms of uncertain behavior and multiple skin cancers is shown at the foot of Table IX.

This increase in the number of cases seen at the regional cancer centres can be attributed in part to the greater occurrence of cancer in the population during the last decade. This increase represents a combination of an increase in population in Ontario, which is also aging, and an increase in smoking-related cancers. It is anticipated that these trends will continue, with an expected annual increase in the absolute number of new cases of cancer requiring treatment.

In Table IX, for 1987, the major sites of newly registered cancers at these centres were breast (18.1%), lung, bronchus and trachea (15.8%), followed by non-melanoma of the skin (9.7%). Of the 21,200 cancers seen for the first time at one of the regional cancer centres or the OCI/PMH, 16.2% were seen in Hamilton, 5.7% in Kingston, 13.5% in London and Ottawa, 1.4% in Sudbury, 2.5% in Thunder Bay, 12.8% at Toronto-Bayview, 4.7% in Windsor, and 29.7% at the Princess Margaret Hospital.

It should be noted that a "new case" registered at a Foundation's regional cancer centre refers to a case of cancer seen for the first time during that year at any one of the Foundation centres. If a case is seen at two cancer centres in the same year, the case is recorded as seen only by the first centre (1.6% of cases were seen at more than two centres in the same year).

The location of the peripheral clinics associated with the regional cancer centres and the OCI/PMH, and the type of outreach program, determine the referral pattern to each (Table X). Thus, in Lambton County, of the 334 cases resident in the county, 317 were referred to the London Centre and only a small number to other centres. On the other hand, in Halton County, of the 599 cases resident in that county,

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*Hospital statistics 1986-1987 published by the Ontario Ministry of Health.

375 were referred to the Hamilton Centre, 198 to OCI/PMH and 20 were referred to the Toronto-Bayview Centre. From the Province of Quebec, 463 residents were referred to Foundation centres; most were seen at the Ottawa Centre. An additional 168 residents of other provinces were seen in Ontario, principally at the OCI/PMH. Of the 154 residents of the USA and other countries treated in Ontario, most were seen at the OCI/PMH, and the Toronto-Bayview and Ottawa Centres.

The data in Tables VIII-X were extracted from the centres in August to September 1988. Data extracted later may differ slightly from those presented here.

Seminar in Cancer Epidemiology

In April 1988, the Epidemiology Research Unit organized a Seminar in Cancer Epidemiology with two sessions: one on screening for cancer, and the other on cancer and occupation. The speakers at the first session were Drs. A.B. Miller, S.D. Walter and E.A. Clarke and, at the second, Drs. H.S. Shannon and J. Siemiatycki.

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We acknowledge with gratitude the continuing co-operation of government. The Ontario Ministry of Health has provided source records and advice; the Office of the Registrar General of the Ministry of Consumer and Commercial Relations has provided computerized data on deaths due to all causes in Ontario residents and, in addition, has provided facilities for an on-site search of their records for treatment evaluation and other research. We appreciate the assistance of the staff of the Hospital Medical Records Institute (HMRI) and are indebted to the medical records staff of all hospitals in Ontario who willingly and promptly provide additional information, primarily for the generation of incidence data, but also to ensure the high quality of data entered in the cancer registry.

We extend a special thanks to the directors of the regional cancer centres and the OCI/PMH and their managers of health records for support during the year, and to the members of the Foundation's Standing Committee on Records and Statistics and its sub-committees.

We acknowledge with gratitude the assistance of all the staff of Information Systems in the processing of the Foundation's large data base. In particular, we thank the individuals working under the direction of Mrs. June Murphy and Mr. Tom Broz.

Our special thanks are extended to Mrs. Mary Nemes, Manager of Provincial Programs Unit in the Division, Miss Darlene Dale, Manager of Operations/Cancer Registration Unit, and the staff of the Division for their dedication to the generation of incidence data and their continual effort to improve the quality of the Ontario Cancer Registry. We are also grateful to Dr. Van C. Nguyen who, with the help of Donna Reynolds, Jean Rowan and Collette Hill, prepared this report.

TABLE VIII*

New Cancer Cases Registered by Treatment Centre, 1978-1987[1,2]

CENTRE	YEAR OF REGISTRATION									
	1978	1979	1980	1981	1982*	1983	1984	1985	1986	1987[3]
Hamilton	2,493	2,594	2,507	2,537	2,688	2,780	2,782	3,498	3,472	3,729
Kingston	1,040	999	984	997	1,073	1,226	1,195	1,238	1,316	1,434
London	2,488	2,537	2,583	2,529	2,563	2,748	2,950	3,080	3,011	3,315
Ottawa	1,902	1,997	2,078	2,190	2,248	2,573	2,847	2,929	2,963	3,117
Sudbury	–	–	–	–	–	–	–	–	285	311
Thunder Bay	412	369	401	462	444	435	506	505	513	552
Toronto-Bayview	–	–	441	504	816	1,251	1,826	2,264	2,774	2,982
Toronto, PMH	6,960	6,911	7,057	7,320	7,012	7,332	7,171	7,328	6,840	6,646
Windsor	854	898	813	907	858	960	1,038	1,053	1,095	1,137
TOTAL	16,149	16,305	16,864	17,446	17,702	19,305	20,315	21,895	22,269	23,223

*Provisional (transition period – see text)

[1] Excludes carcinoma of cervix in situ.

[2] Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

[3] Data extracted from the centres in August or September 1988.

TABLE IX

New Cancer Cases Registered by Site of Disease and Treatment Centre, 1987[1]

SITE OF DISEASE	ICD9[2] NUMBER	TREATMENT CENTRE									TOTAL	
		Hamilton	Kingston	London	Ottawa	Sutbury	Thunder Bay	Toronto		Windsor	Number	Per Cent
								Bayview	PMH			
Lip	140	14	12	18	6	–	–	3	15	4	72	0.3%
Tongue	141	25	11	27	24	–	–	14	77	7	185	0.9%
Rest of mouth	142-145	33	11	63	45	–	8	43	111	11	325	1.5%
Pharynx and tonsil	146-149	36	19	36	40	–	5	34	130	14	314	1.5%
Esophagus	150	36	9	33	28	1	7	28	83	11	236	1.1%
Stomach	151	61	4	32	51	6	9	30	51	23	267	1.3%
Intestine, except rectum	152-153	125	46	123	171	13	23	72	214	47	834	3.9%
Rectum and anal canal	154	118	35	85	99	3	27	58	273	41	739	3.5%
Other digestive system	155-159	59	17	27	63	8	14	38	58	30	314	1.5%
Nose, middle ear and accessory sinuses	160	7	2	8	7	–	–	8	25	2	59	0.3%
Larynx	161	55	17	49	69	1	11	35	182	17	436	2.1%
Lung, bronchus and trachea	162	502	230	421	479	66	87	451	966	144	3,346	15.8%
Other respiratory	163-165	17	19	15	10	3	3	9	17	1	94	0.4%
Bone	170	8	5	3	11	4	1	10	6	4	52	0.2%
Malignant melanoma	172	113	15	63	70	7	8	190	145	27	638	3.0%
Other cancer of skin	173	309	207	312	170	2	51	454	388	153	2,046	9.7%
Breast	174-175	596	198	544	536	61	87	474	1,195	155	3,846	18.1%
Cervix uteri	180	66	20	63	60	5	7	42	189	8	460	2.2%
Other uterus	179,181,182	138	44	101	108	6	12	50	229	19	707	3.3%
Ovary, tubes and ligament	183	88	20	65	52	9	11	37	161	15	458	2.2%
Other female genital organs	184	28	3	5	8	–	1	12	34	5	96	0.5%
Prostate	185	193	71	184	143	8	40	136	304	59	1,138	5.4%
Testis	186	33	13	21	24	1	4	24	95	14	229	1.1%
Other male genital organs	187	4	1	–	5	–	1	5	8	–	24	0.1%
Bladder	188	65	21	47	82	1	10	39	139	25	429	2.0%
Kidney and other urinary	189	38	14	24	62	8	8	41	70	11	276	1.3%
Brain and nervous sytem	191-192	58	21	81	64	4	6	74	136	16	460	2.2%
Thyroid gland	193	8	4	8	7	–	2	3	42	2	76	0.4%
Lymphosarcoma and reticulum cell sarcoma	200	50	26	81	63	14	13	58	168	21	494	2.3%
Hodgkin's disease	201	45	10	30	37	8	6	43	116	12	307	1.4%
Other lymphomas	202	122	18	51	64	19	13	37	120	22	466	2.2%
Leukemia	204-208	94	33	74	45	24	16	56	144	33	519	2.4%
Other sites	Residual	284	37	160	149	24	38	102	409	55	1,258	5.9%
TOTAL MALIGNANT		3,428	1,213	2,854	2,852	306	529	2,710	6,300	1,008	21,200	100.0%
Cervix uteris (in-situ)	233.1	–	2	1	6	–	1	–	7	–	17	
Other sites (in-situ)	230-234	50	38	72	35	1	6	73	83	26	384	
Neoplasms of uncertain behavior	235-238	38	12	41	25	3	9	15	54	12	209	
Multiple skins (see text)	173	213	171	348	205	1	8	184	209	91	1,430	
Seen at more than one centre		6	11	107	41	8	1	54	103	7	338	

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[1] Data extracted from the Centres in August or September, 1988.

[2] ICD9 – International Classification of Diseases, Ninth Revision, World Health Organization Geneva, 1977.

TABLE X

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1987*

COUNTY OR DISTRICT	TREATMENT CENTRE									TOTAL
	Hamilton	Kingston	London	Ottawa	Sudbury	Thunder Bay	Toronto		Windsor	
							Bayview	PMH		
Algoma	2	–	6	1	9	5	7	126	1	157
Brant	225	–	11	–	–	–	–	5	–	241
Bruce	6	–	136	–	1	–	4	25	–	172
Carleton	2	5	3	1,513	–	1	13	7	–	1,544
Cochrane	8	–	6	18	11	4	12	115	–	174
Dufferin	2	–	3	–	–	–	3	37	1	46
Dundas	–	2	–	59	–	–	–	1	–	62
Durham²	2	2	1	–	–	–	93	349	–	447
Elgin	–	–	171	–	–	–	–	1	1	173
Essex	–	1	70	2	2	–	3	11	942	1,031
Frontenac	1	392	–	7	–	–	4	10	1	415
Glengarry	–	1	–	46	–	–	–	–	–	47
Grenville	–	36	–	49	–	–	–	–	–	85
Grey	1	–	168	–	2	–	3	55	–	229
Haldimand-Norfolk¹	149	–	58	–	–	–	2	3	–	212
Haliburton	2	–	–	1	–	–	6	28	–	37
Halton	375	1	–	5	–	–	20	198	–	599
Hastings	1	276	–	6	–	–	30	59	–	372
Huron	–		148	–	–	–	–	3	–	151
Kenora	–	–	–	–	–	33	1	4	–	38
Kent	–	–	222	–	–	–	2	3	24	251
Lambton	–	–	317	1	–	–	4	11	1	334
Lanark	–	40	–	116	–	–	1	1	1	159
Leeds	–	171	–	11	–	–	1	1	–	184
Lennox and Addington	1	105	–	5	–	–	2	1	–	114
Manitoulin	–	–	–	2	8	–	–	12	–	22
Middlesex	–	–	829	1	1	–	2	7	2	842
Muskoka	2	–	4	1	–	–	17	85	1	110
Niagara¹	810	1	5	–	–	1	20	89	–	926
Nipissing	–	1	3	4	5	1	7	158	1	180
Northumberland²	–	21	1	–	–	–	34	109	–	165
Oxford	2	–	201	–	–	–	–	9	–	212
Parry Sound	2	–	1	3	4	–	13	73	–	96
Peel	11	1	1	–	1	–	135	597	–	746
Perth	1	–	160	1	–	1	–	1	–	164

TABLE X (Continued)

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1987*

COUNTY OR DISTRICT	TREATMENT CENTRE									TOTAL
	Hamilton	Kingston	London	Ottawa	Sudbury	Thunder Bay	Toronto		Windsor	
							Bayview	PMH		
Peterborough[1]	1	1	1	1	–	–	34	204	–	242
Prescott	–	–	–	60	–	–	–	–	–	60
Prince Edward	–	81	1	1	–	–	7	7	–	97
Rainy River	–	–	–	–	–	42	–	–	–	42
Renfrew	–	–	–	220	–	–	–	4	–	224
Russell	–	–	–	47	–	–	–	–	–	47
Simcoe[2]	1	5	4	3	1	–	150	318	1	483
Stormont	–	12	–	136	–	–	–	–	–	148
Sudbury	2	1	4	7	247	–	11	221	–	493
Thunder Bay	8	1	3	–	–	437	6	25	–	480
Timiskaming	4	1	2	6	8	2	3	56	–	82
Victoria[2]	1	–	2	1	–	–	31	93	–	128
Waterloo	176	–	242	–	–	–	8	49	–	475
Wellington	199	1	39	1	2	–	13	26	–	281
Wentworth	1,137	2	1	–	1	–	10	11	–	1,160
York	6	5	5	7	2	–	1,893	2,933	1	4,852
Quebec	1	7	3	433	–	–	8	10	1	463
Other Provinces	5	13	10	40	–	1	17	78	4	168
U.S.A.	4	15	5	11	–	1	10	8	10	64
Other World	–	2	6	18	–	–	23	37	4	90
Residence at diagnosis not stated	278	10	1	8	1	–	47	26	11	382
TOTAL	3,428	1,213	2,854	2,852	306	529	2,710	6,300	1,008	21,200

*Data extracted from the Centres in August or September, 1988.

[1] In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.

[2] In 1974 the counties of Durham and Ontario became the Durham Regional Municipality. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expand by parts of Durham and Ontario.

[3] In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand-Norfolk.

INFORMATION SYSTEMS

OVERVIEW OF INFORMATION SYSTEMS

J.I MURPHY, B.A.[*], E.A. MURPHY[**], T. BROZ, B.Sc., B.Comm.[†]
and T.N. HUANG, B.Sc.[††], *Toronto, Ontario*

In 1987, Information Systems (IS) developed its first strategic plan covering the period 1987 to 1990; its principal emphasis was the new technologies needed for the Regional Cancer Centres and the Ontario Cancer Registry. That document has been revised to include plans for financial and human resources systems and has been extended to 1991.

The plan describes a common Foundation approach to the delivery of computing resources; its ultimate goals are:

- To provide the ability to communicate across facilities and to optimize data storage.
- To allow easy access to information for users and to provide them with good analysis tools.
- To provide the Regional Cancer Centres with the ability to customize their systems and to satisfy unique local requirements.
- To provide the ability to use externally developed software.
- To position the Foundation to meet future demands and take advantage of future technologies.

The plan includes an overall process for the creation of the necessary computing environments for Information Systems' three major users: the Regional Cancer Centres, the Division of Epidemiology and Statistics, and the Financial/Administration Departments.

The first step in this process is the definition of user requirements. In 1987, Honeywell Bull consultants completed the requirements for a new oncology patient information system (OPIS). In mid-1988, a team from the Division of Epidemiology and Statistics and from Information Systems completed requirements for an integrated Registry system. Finally, a consultant from Stratsystem was engaged to create a business model for financial and human resources systems.

A consultant from The Transition Group Inc. described the communications technology which would link together the organization's computers and allow interactions with external computers. Fig. 1 shows a schematic of the proposed network.

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[*] Manager, Information Systems.

[**] Systems Manager, Patient Care and Corporate Systems.

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[††] Systems Manager, Technology Support and Operations.

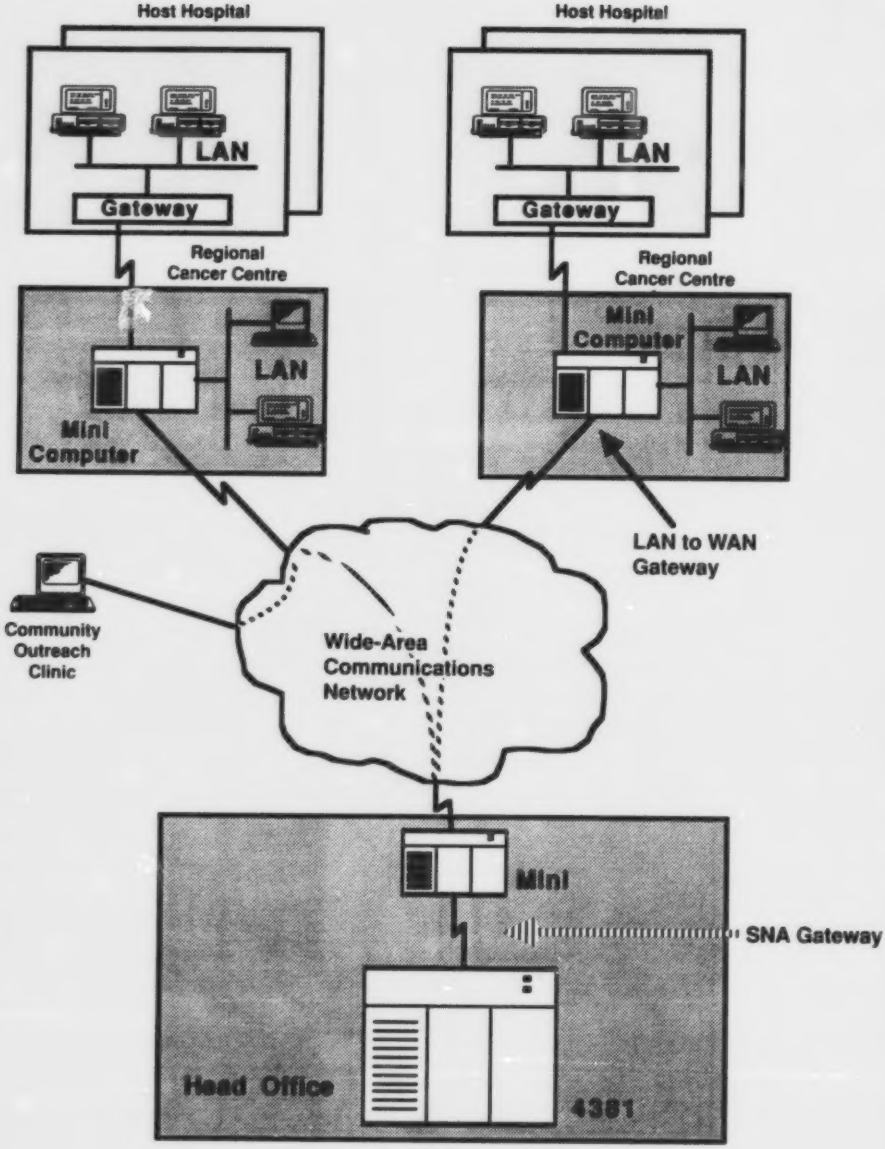
Host Hospital
Host Hospital
LAN
LAN
Gateway
Gateway
Regional Cancer Centre
Regional Cancer Centre
Mini Computer
Mini Computer
LAN
LAN
LAN to WAN Gateway
Community Outreach Clinic
Wide-Area Communications Network
Mini
SNA Gateway
Head Office
4381

Fig. 1 Topology of communications network linking cancer centres with outreach clinics, host hospitals and the OCTRF Head Office.

After the requirements have been defined, the next step is to determine the appropriate hardware and software technologies. In December 1987, in a "request for proposal" issued to appropriate vendors, the Foundation invited recommendations concerning the Regional Cancer Centres' hardware, software and communications requirements. In May 1988, the Committee on Information Systems accepted Digital Equipment Corporation (DEC) as the vendor of record for computer hardware and software for the new Centre system, including the communication network.

ORACLE, a relational database, has been selected as the data management system. The specific details of the environment in each location remain to be determined. However, Information Systems has installed an interim development machine, a Digital MicroVAX 3600, so that its staff can begin to develop the OPIS, while a complete implementation plan is being defined. The overall approach is as follows:

- Appropriate models of Digital MicroVAX computers will be installed in each Centre. Eventually these will act as "distributed" computers to each Centre's host-hospital computer system.
- The facilities of each Centre also will include an ETHERNET DECNET LAN, which will allow any terminal of PC in the Centres to access the MicroVAX.
- A Centre and its host hospital will be connected via the DECNET, wide-area communications network (WAN). The Centre's LAN will have appropriate interface hardware and sofware "gateways" to connect it to the host hospital's computer. These gateways may vary depending on the technical requirements for connecting with each particular host hospital's configuration.
- IBM will continue to supply the hardware for the Registry. In mid-1987 we acquired an IBM 4381 model, which was an upgrade to model 91E in late 1988. This system can continue to expand to handle the Registry's requirements for the next five to seven years. This IBM mainframe also will be attached to the Foundation's new communications network. We have selected a relational database, DB2, a product from IBM, to manage the storage of the Registry data.

The development teams of both OPIS and the Registry system had to learn the new technologies, and the department had to create new methods of software development to take advantage of these new technologies. The following subsections briefly describe the specific activities related to each major user area.

ONCOLOGY PATIENT INFORMATION SYSTEM

The current PCMS system is being replaced because it cannot be enhanced to meet the increasing needs of the centres. The seven-year-old hardware and operating software are restrictive and hence do not provide easy access to the wealth of data being stored on our databases. These problems will be remedied when we implement a new hardware/software technology platform and the new OPIS application.

The OPIS development plan is built in phases. Phase I will replace the old system and provide database access to all users. In addition to the system architecture -- database design, system support utilities and security system -- the major components of Phase I are: central patient index (CPI); disease registration (case); workload; chart tracking; scheduling; progress notes; letter follow-up; and treatment recording.

It will offer a "select" capability that includes the ability to download data to the PCs on the LAN for use as study files (using SAS or MEDLOG). Also, Phase I would ensure that there are appropriate "hooks" to add billing, either as part of OPIS or by leaving it operating on PCs (as is done at present) but using the OPIS patient data. Subsequent phases, to be defined later, will include clinical studies and integration of hospital data into a mini chart.

Hospital-system-based functions such as order entry-results reporting, radiology, pharmacy, bed census, supplies ordering, etc., will remain on the hospital system. We intend only to provide a facility so that the same "screen" can access both OPIS and the hospital systems; thus a user will not need an OPIS terminal, a hospital system terminal and a PC in order to make full use of the available systems.

We plan that Phase I -- the core OPIS system -- will be implemented in the fourth quarter of 1989; the Toronto-Bayview Centre will act as the pilot site.

The requirements for OPIS are being translated into a viable system by a team composed of systems professionals in Information Systems and a User Interface Committee (UIC). The members of the UIC are:

Denise Armstrong
Manager, Health Records
Hamilton Centre

Nancy Hobbs
Head Technologist
Kingston Centre

Dr. Walter Kocha
Medical Oncologist
London Centre

Micheline Mistruzzi
Manager, Health Records
Toronto-Bayview Centre

Carolynn Weatherbie
Computer Co-ordinator
Ottawa Centre

Mary Nemes
Manager, Provincial Programs
Head Office, Toronto

Periodically the IS staff and the UIC meet with representatives from all the centres for workshops, which review the system and reach a consensus that the system will meet the needs of all the centres.

We are grateful to the members of the UIC and all those who have attended workshops. Their interest and dedication will ensure the success of OPIS.

Linkage

In conjunction with the Division of Epidemiology and Statistics, we completed four record linkages so that we can generate 1986 incidence data by the end of 1988.

(i) The death clearance linkage -- a major project, which included all the death certificate data from the years 1964 to 1986 -- indicates which cancer patients have died. This is the first time deaths from all causes were included in a linkage with the Registry database. The results of this linkage are as follows:

Patients in 1964-1985 incidence file	645,843
Death certificates in 1964-1986 death file	1,392,000
Number of death certificates linking to the incidence file	367,565

(ii) The 1986 hospital discharge records for patients with a diagnosis of cancer were linked internally to bring together multiple admissions of the same patient.

(iii) Pathology reports indicating a diagnosis of cancer then were linked to the hospital discharges to create a preliminary 1986 incidence file.

(iv) Finally, this file was linked with the 1964-1985 incidence file adding 1986 cases.

The Ontario Cancer Registry (OCR) file contains a proportion of cases where the patient's residence code either is unknown or is incomplete. Using record linkage, we obtained the address histories of all cancer patients, who are also licensed drivers, from the Ministry of Transportation and Communications license database.

The strategic plans of both the Division of Epidemiology and Statistics and Information Systems aim to reduce the lead time needed to make the incidence data available. In 1989, a specific objective is to reduce that time from 24 to 21 months by having 1987 incidence data available by September 1989.

Systems and Database

In the last few years, we have developed a number of systems and programs and now it is desirable to consolidate and integrate the various components. The integrated system will make full use of a relational database (DB2), with applications available on line, where required. The first phase of this development will convert the data-entry systems for pathology, steroid receptors and death from the Honeywell computer to DB2 on the IBM 4381 computer.

We have made availabe the Registry incidence and mortality master files for on-line viewing. The data, which are stored in DB2, can be accessed through patient inquiry application or IBM's query management facility. The application allows the user to retrieve data, for example, by surname/given-names/birthdate or by site-diagnosis/year/sex/age/vital-status/residence/country etc. Whenever new data are available, both databases will be reloaded.

In 1988, we established a database development group to create the database design for the integrated system. This group is responsible for the creation and implementation of procedures and policies affecting database access, data naming, database and software backup/recovery, and performance.

We have developed a conceptual data model to ensure that all data and its significance to the Registry systems are properly understood. It will be used as a logical blueprint for physical database design for the integrated Registry system.

SUPPORT AND SERVICES

In 1988, to better serve the needs of the Division of Epidemiology and Statistics, Information Systems established the Registry Support and Services Centre. The centre is operated by a group dedicated to providing prompt and effective data-processing-related support and services including information retrieval, request handling, training, consulting, "troublelshooting", technical support, access to equipment and software.

In addition, Information Systems have supported many special projects undertaken by the Division of Epidemiology and Statistics such as a quality control study of patients who were treated at a Metropolitan Toronto hospital and were diagnosed in 1982 with cancer in the 150-159 ICD9 site range (GI tract).

FINANCE AND HUMAN RESOURCES

Financial, human resources and other administrative systems will be acquired or developed in co-operation with the Ontario Cancer Institute. The Foundation has undertaken a requirements study for these systems and the centres will be involved in much the same way they were for the Honeywell study.

Following completion of the study, available application packages will be evaluated, selected and implemented based on the Foundation's priorities established during the requirements study.

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APPENDICES

APPENDIX A

BEQUESTS AND OTHER DONATIONS

The Foundation was the grateful recipient of legacies, bequests and other donations totalling $1,496,987 for the fiscal year ending March 31, 1988, which are of inestimable value to the Foundation's program.

Legacies of $1,000 or over were received during the above period from the following estates:

The late Frederick Robert Abercrombie, Islington	$ 10,000
— Jack McAdam Aiken, Orangeville	3,000
— Emily Parkes Boal, Perth	5,000
— Jennie P. Breindahl, Ottawa for use at Ottawa Centre	3,886
— Ethel Bremner, Toronto for research	3,264
— Ada May Brunner, Thamesville for research at London Centre	4,375
— Ina Bugg, London for use at London Centre	8,250
— Nellie Burke, Toronto	2,000
— Flossie Bell Choate, Mississauga	2,000
— Ethel Jane Cowan, Drumbo for use at Windsor Centre	2,000
— Jessie Isabella Cowan, Drumbo for use at Windsor Centre	2,000
— Mary E. Cunningham, London for use at London Centre	3,051
— Dorothy May Denmark, Ottawa	1,962
— Mabel Dillman, Newmarket	2,000
— Dorothy Evelyn Douglas, Thunder Bay	51,280
— Eldred Durham, Toronto (Anne and Eldred Durham Trust Fund) for research	6,782
— Lionel Lambert Fabian, Toronto	5,000
— John Jacob Freedman, Toronto	6,000
— Agnes Gaukel, Scarborough	7,297

— Erma Zoe Louise Goering, Hamilton for research at Hamilton Centre	3,900
— William John Hanley, York	172,845
— Mary Margaret Harbour, Etobicoke	7,933
— William Hirsch, North York	1,737
— Florence Hunter, Hamilton	29,546
— Mabel Matilda Kelly, London for use at London Centre	31,750
— Eileen Law, Richmond Hill for research	2,067
— Jeanie Smith Macdonald, Thunder Bay for use at Thunder Bay Centre	1,000
— Elizabeth Annie Marchment, Brampton	3,006
— Bea Rose Masse, Sarnia for use at Windsor Centre	1,400
— Robert Pickard McBride, Hamilton	66,200
— Alice M. McMillan, Kingston for use at Kingston Centre - 500 for research at Kingston Centre - 1,100	1,600
— Archibald Mitchell, London for use at London Centre	19,875
— John Elwood Morrison, Etobicoke	10,000
— Ena Beatrice Nelson, London	21,000
— Eva Josephine Cordingley Porter, Hamilton	64,992
— John Bruce Archer Reeson, Oshawa	100,000
— Bertha Mabel Richter, London (Richter Endowment Fund Trust) for use at London Centre	138,000
— Marion Claire Robinson, Ingersoll	50,000
— Joan Alison Sanborn, Toronto	46,000
— Clara Bell Sanderson, Brantford	9,977
— Marjorie Evelyn Sharpe, Caledon	10,000
— Lewis Taylor, Goderich	40,000
— Flossie Irene Tilson, Brampton	120,000
— Beatrice Tufts, Amherstburg for use at Windsor Centre	5,376
— Evan Rudolph Waldon, Cobourg	4,516
— Lena West, Newmarket	9,688
— Hazel Adelaide Whitley, Shelburne	18,143
— Marjorie Wilson, Pickering	34,526

Donations of $1,000 or more were received from the following:

— Louis Aldrovandi, Woodbridge for purchase of Pain Pump for Toronto-Bayview Centre	3,395
— Anonymous, Ottawa for research at Ottawa Centre	2,000
— Anonymous, Unionville for research at Toronto-Bayview Centre	1,000
— Beta Sigma Fi, Windsor toward purchase of CADD-PCA Pump for Windsor Centre	2,237
— Charles Braham, Jarvis in memory of Gladys Braham for use at Hamilton Centre	1,000
— Bernard Cheung and Friends, Toronto in memory of Dorothy Cheung	1,000
— Joseph P. Crothers, Willowdale for research at Toronto-Bayview Centre	1,000
— Mrs. Jean R. Cuddy, Toronto for Pain Pump Program at Toronto-Bayview Centre	3,400
— Elbertson Industries Ltd., Kingston for special services for patients at Kingston Centre	5,000
— Lorraine Ferguson, Tupperville for use at London Centre	1,000
— Walter Fischer, Kitchener for use at Thameswood Lodge, London	2,500
— Forest City Youth Slo-Pitch Assoc., Inc., London for purchase of video equipment for London Centre	1,800
— Anna Gluschuk, London for research at London Centre	1,000
— John W. Grand, Toronto for research at Toronto-Bayview Centre	2,000
— James H. Gregory, Kingston to refurbish Cancer Research Room at Kingston Centre	5,000
— A.C. Hamilton, Toronto for Pain Pump Program at Toronto-Bayview Centre	3,400
— Jean Hogan, Kingston for use at Kingston Centre	1,000

— I.C.I. Pharma (Atkemix Inc.), Mississauga for research	1,800
— Jones Box and Label Co. Ltd., London for research at London Centre	1,000
— Mrs. Winnifred Kerr, Dundas for use at Hamilton Centre	1,000
— Kodak Canada Inc., Ottawa for use at Ottawa Centre	10,000
— Ladies' Auxiliary, Martello Unit #377, Kingston for use at Kingston Centre	1,000
— Dina Minardi, Copper Cliff for use at Kingston Centre	1,000
— The Oshawa Group Limited, Islington	2,715
— M.& A. Paolucci Charitable Foundation, Willowdale	1,000
— Reitzel Rentals, Division of Reitzel Bros. Ltd., Kitchener for research at London Centre	7,500
— Employees of Royal Bank of Canada, Toronto — Main Branch	1,218
— St. Clair Ladies Club, Windsor for purchase of CADD-PCA Pump for Windsor Centre	1,000
— Joseph Schwartz, Cambridge for use at Thameswood Lodge, London	5,000
— Dorothy and Donald Scott, Waterloo for research in neuro-oncology at London Centre	6,000
— Paul Scott, Sarnia for research in medical oncology at London Centre	1,000
— The Sisk Brothers, Mississauga, Fredericton, Napierville and Ottawa for use in medical oncology research at Ottawa Centre	1,000
— Ila M. Stewart, London for research in neuro-oncology at London Centre	10,000
— Wilson M. Stewart, Ottawa for radiotherapeutic research at Ottawa Centre	1,000
— Superior Propane Inc., Concord for Pain Pump Program at Toronto-Bayview Centre	3,500

— Mrs. Ruth Tam, Mitchell for use at Thameswood Lodge, London	1,500
— J. Hiles Templin, Burlington for purchase of two wheelchairs for the Hamilton Centre	1,000
— The Toronto Star, Toronto	1,000
— Valley East Volunteer Fire Fighters Assoc., Val Therese for purchase of Pain Pump for Northeastern Ontario Oncology Program in Sudbury	1,053
— Barbara Vanicek, Thornhill for Pain Pump Program at Toronto-Bayview Centre	1,000
— Mr. and Mrs. Donald Whatman, London for research at London Centre	1,000

The Foundation is grateful to these donors and to the many others not listed above and it reveres the memory of those who, when making their wills, extended beyond their lifetime the fight against cancer. These welcome additions to our research program and other funds ensure that the Foundation's extensive research program can proceed at a time of financial constraints and inflated costs.

APPENDIX B

LIST OF ARTICLES PUBLISHED IN 1987 BY CAREER SCIENTISTS, RESEARCH ASSOCIATES, GRANTEES, MEMBERS OF THE OCTRF STAFFS AT THE REGIONAL CANCER CENTRES AND HEAD OFFICE AND THE OCI/PMH

HAMILTON

OCTRF Hamilton Regional Cancer Centre:

BROWMAN GP, LEVINE MN, RUSSELL R, GOODYEAR M, ARCHIBALD S, JACKSON S, YOUNG JEM: Randomized trial of simultaneous versus 18-hour sequential methotrexate and 5-fluro-uracil in head and neck cancer. *Proc Am Soc Clin Oncol* 1987; **6:** 123. (Abstract 481)

BROWMAN GP, PRIORE R, AZARNIA N, et al: Predictors of response to low dose ara-C. *J Cell Biochem* 1987; **11**(Suppl A): 236.

DOYLE DJ, TURPIE AGG, HIRSH J, BEST C, KINCH D, LEVINE MN, GENT M: A randomized trial of adjusted subcutaneous heparin versus continuous intravenous heparin in patients with acute deep vein thrombosis. *Ann Intern Med* 1987; **107**: 441.

HIRSH J, LEVINE MN: The optimal intensity of oral anticoagulant therapy. *JAMA* 1987; **258**: 2723.

HIRSH J, OFOSU FA, LEVINE M: The development of low molecular weight heparins for clinical use. *In:* Verstraete M, Vermylen J, Lijnen R, Arnout J, eds. Thrombosis and Hemostasis. Leuven: Holland, Leuven University Press, 1987: 325.

LEVINE MN, ARNOLD A, BUSH H, ABU-ZAHRA H, DePAUW S: Quality of life (QL) in Stage II breast cancer: An instrument for clinical trials. *Proc Am Soc Clin Oncol* 1987; **6**: 254. (Abstract 999)

LEVINE MN, ARNOLD A, KELLEHER L, LORD S, HRYNIUK W, HIRSH J: Cancer chemotherapy and thrombosis. *Thromb Haemost* 1987; **6:** 404.

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